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Review article

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Intracerebral haemorrhage — mechanisms, diagnosis and prospects for treatment and prevention

David J. Seiffge[1,7], Simon Fandler-Höfler[2,3,7], Yang Du[2,4], Martina B. Goeldlin[1], Wilmar M. T. Jolink[5], Catharina J. M. Klijn[6,7] & David J. Werring[2,7]

Abstract

Intracerebral haemorrhage (ICH) is a devastating condition associated with high mortality and substantial residual disability among survivors. Effective treatments for the acute stages of ICH are limited. However, promising findings from randomized trials of therapeutic strategies, including acute care bundles that target anticoagulation therapies, blood pressure control and other physiological parameters, and trials of minimally invasive neurosurgical procedures have led to renewed optimism that patient outcomes can be improved. Currently ongoing areas of research for acute treatment include anti-inflammatory and haemostatic treatments. The implementation of effective secondary prevention strategies requires an understanding of the aetiology of ICH, which involves vascular and brain parenchymal imaging; the use of neuroimaging markers of cerebral small vessel disease improves classification with prognostic relevance. Other data underline the importance of preventing not only recurrent ICH but also ischaemic stroke and cardiovascular events in survivors of ICH. Ongoing and planned randomized controlled trials will assess the efficacy of prevention strategies, including antiplatelet agents, oral anticoagulants or left atrial appendage occlusion (in patients with concomitant atrial fibrillation), and optimal management of long-term blood pressure and statin use. Together, these advances herald a new era of improved understanding and effective interventions to reduce the burden of ICH.

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A full list of affiliations appears at the end of the paper. e-mail: d.werring@ucl.ac.uk

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Key points

- Intracerebral haemorrhage (ICH) is a common and severe type of stroke associated with severe morbidity and mortality.
- Advances in acute treatment of ICH, including ultra-early blood pressure control, anticoagulation reversal and minimally invasive neurosurgical procedures, have great potential to improve patient outcomes; bundled approaches might have particular value in acute settings.
- Diagnosis of the underlying aetiology of ICH is crucial for understanding the cause; diagnosis usually requires both vascular and structural (magnetic resonance) imaging.
- The most important aetiologies of ICH include arteriolosclerosis, cerebral amyloid angiopathy and macrovascular causes.
- ICH aetiology must be determined to assess the risk of recurrent ICH and other vascular events, which informs the use of individualized secondary prevention strategies and decisions on the use of antiplatelet or anticoagulant treatments for other indications.

Introduction

In 2019, 27% of all incident strokes globally were caused by intracerebral haemorrhage (ICH), affecting a total of 3.41 million people[1]. These ICH events accounted for 68 million disability-adjusted life years lost, resulting in a greater disease burden than ischaemic stroke[1]. ICH continues to be associated with marked mortality and morbidity, with population-based studies reporting a case fatality rate of 40% at 1 month[2], and 1-year and 5-year survival rates of 46% and 29%, respectively[3]. Contemporary hospital-based cohorts report that only a third of people with ICH are functionally independent 3 months after the stroke event[4].

The trajectory of functional recovery after ICH is perceived by some experts to differ from that of ischaemic stroke, with a slower rate of recovery, although systematic studies that support this observation are lacking. Nevertheless, post hoc analyses of randomized controlled trials from the past couple of years have shown that people with ICH can experience considerable functional improvement up to 12 months after injury — well beyond the acute phase — particularly among those with poor early outcomes at 30 days, implying that rehabilitation measures should be offered well beyond the first 6 months following ICH[5,6]. Outcome research in ICH has increasingly focused on previously neglected but important non-motor outcomes[7]. Long-term functional decline, cognitive decline and post-ICH dementia are frequent in cohort studies with survivors of ICH[8–11]. Moreover, compared with people with ischaemic stroke, anxiety, reduced participation in social roles and activities, fatigue, pain and impaired bowel function are all substantially more common in people with ICH, suggesting an urgent need for further longer-term studies in survivors of ICH[7].

Despite considerable breakthroughs in the management of ischaemic stroke, progress in the management of ICH has not kept pace. Overall, functional outcomes after ICH are perceived to be poorer than those after ischaemic stroke[12] although systematic, large-scale, prospective population-based data are lacking[2,3,13]. Moreover, therapeutic trials in ICH have failed to provide high-level evidence of treatment efficacy, probably in part owing to recruitment challenges leading to small sample sizes and a high risk of bias[14]. However, despite the continued widespread perception that ICH is a largely untreatable disease, considerable advances in our understanding and management of ICH have been made in the past few years, reigniting optimism that new treatment approaches might finally lead to improved outcomes after ICH. In this Review, we provide an update on key advances and remaining uncertainties in ICH management related to diagnosis, aetiology, acute therapy and secondary prevention.

Key advances in diagnosis and aetiology

Diagnosing causes of intracerebral haemorrhage

ICH can be caused by a diverse range of conditions. Rapid and accurate diagnosis of ICH and its underlying aetiology is essential to guide rational acute treatment, prognosis and prevention strategies.

Approximately 80% of ICHs among adults aged 50 years or older are caused by cerebral small vessel disease (SVD)[4] — mainly cerebral amyloid angiopathy (CAA) and arteriolosclerosis (also termed deep perforator arteriopathy or 'hypertensive arteriopathy')[15] (Fig. 1). In terms of prognosis, ICH due to CAA is consistently associated with a much higher risk of ICH recurrence than is arteriolosclerosis (7.4–8.5% versus ~1.0–1.7% per year)[16–18]. The underlying arteriopathy might also influence the risk of ischaemic vascular events, including ischaemic stroke, which is higher than the risk of recurrent ICH for people with ICH attributable to arteriolosclerosis (4.3% versus 1.1% at 3 months)[19]. The early risk of ischaemic stroke in people with ICH attributable to arteriosclerosis is as high as in people with lacunar ischaemic stroke (4.3% for ICH attributable to arteriolosclerosis versus 2.9% for people with lacunar stroke 3 months after the index event)[19], an observation of potential relevance to guide secondary preventive strategies. A subset (~10–20%) of ICH is related to macrovascular causes[4,16,20–22], including arteriovenous malformation and fistula, aneurysm, cavernous malformation and cerebral venous sinus thrombosis. Rapid diagnosis of a macrovascular cause of ICH might enable immediate intervention and guide decisions for subsequent management. Other, rarer, underlying causes that might warrant specific treatments include cerebral venous sinus thrombosis, vasculitis, reversible cerebral vasoconstriction syndrome and moyamoya disease. As patient characteristics (for example, age and ICH location) cannot reliably predict the underlying cause[23], acute diagnostic work-up for ICH should usually include imaging of the brain parenchyma and intracranial vasculature.

CT (or magnetic resonance) angiography is usually the first step in the investigation of possible macrovascular causes of ICH, and has reasonably high diagnostic accuracy compared with acute intra-arterial digital subtraction angiography[24]. However, CT angiography might miss small arteriovenous malformations and fistulae[24]. The reference standard for the detection of macrovascular causes of ICH is intra-arterial digital subtraction angiography; however, this procedure is invasive, requires interventional neuroradiologist expertise and is associated with complications, such as access site haematoma and cerebral ischaemia; the risk of such complications in people with ICH who undergo this procedure is reported to be 3–5%[25,26]. Intra-arterial digital subtraction angiography should therefore be performed only when the level of suspicion for a macrovascular cause is likely to outweigh the procedural risks. The DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) and DIAGRAM+ scores (Box 1) can be used to determine the probability of an underlying macrovascular cause in people with ICH[27]. Of note, however, the DIAGRAM score was developed on the basis of data from a prospectively collected cohort

of people aged 18–70 years, and excluded those aged >45 years with hypertension and ICH in the basal ganglia, thalamus or posterior fossa[24]. In addition, diagnoses of SVD in the DIAGRAM study were based on CT and not MRI, which is superior to CT in assessing the presence and severity of underlying SVD, and might have improved diagnostic value in the context of identifying or excluding a macrovascular cause. Indeed, a study published in 2024 (ref. 28) suggests improved diagnostic accuracy for macrovascular causes of ICH using the MRI-based MACRO score. The utility of more advanced non-invasive imaging techniques (such as dynamic 4D-CT angiography, or dynamic 4D magnetic resonance angiography) for the diagnosis of macrovascular causes of ICH requires further investigation.

Arteriolosclerosis is the most frequent SVD that causes ICH, being responsible for >90% of non-lobar ICH cases as well as about half of lobar ICH cases on the basis of data from in vivo neuroimaging[17,29] and post-mortem histopathology studies[30]. Several groups have proposed imaging-based criteria for arteriolosclerosis[17,29,31]. Histopathological validation is available for most of the individual markers of SVD[32], but not yet for any set of specific diagnostic criteria for arteriolosclerosis, perhaps owing to the heterogeneity of histopathological findings; this heterogeneity contrasts, for example, with sporadic CAA, in which the hallmark finding is small vessel wall amyloid-β deposition[33]. The use of a standardized neuroimaging definition for arteriolosclerosis-related ICH, including combinations of lacunes, moderate or severe periventricular white matter hyperintensities and non-lobar (deep) haemorrhages (ICH or cerebral microbleeds), could improve pathophysiological understanding and comparability across studies.

CAA is responsible for most of the other ~50% of lobar ICH cases[30,34] and can be diagnosed with high diagnostic accuracy in people with ICH using acute CT (Edinburgh criteria[30]) or MRI (Boston 2.0 criteria[35]). The Edinburgh criteria use two specific CT-defined neuroimaging haematoma characteristics (finger-like projections and subarachnoid extension) and the *APOE* genotype. The Boston criteria for CAA[36] use MRI-defined haemorrhagic lesions, including strictly lobar cerebral microbleeds, ICH, cortical superficial siderosis and convexity subarachnoid haemorrhage. The latest update of the Boston criteria includes two additional non-haemorrhagic MRI markers: significant burden of MRI-visible perivascular spaces in the centrum semiovale; and white matter hyperintensities in a 'multispot pattern'. These additions increase sensitivity without compromising specificity, particularly in non-ICH presentations[35].

One unresolved aspect of SVD classification is that of a 'mixed' pattern of neuroimaging markers associated with CAA and arteriolosclerosis in the same individual. Whether this pattern truly indicates 'mixed' CAA and arteriolosclerosis or widespread arteriolosclerosis in deep and lobar small vessels remains uncertain; the latter suggestion is supported by a 2023 MRI-pathological study[37], which showed that strictly lobar cerebral microbleeds can, in some cases, be caused by arteriolosclerosis, and cohort studies suggesting that people with a 'mixed' pattern of ICH have a similar risk factor profile to that of ICH associated with arteriolosclerosis[16,17,38]. Furthermore, the lobar cerebral microbleeds in CAA might be cortical rather than juxtacortical[39], which, if confirmed, could more accurately determine the relative contributions of each arteriopathy to lobar cerebral microbleeds. Cortical superficial siderosis seems to be highly specific for CAA[36], suggesting the presence of true 'mixed' CAA and arteriolosclerosis in patients with lobar and deep cerebral microbleeds, ICH, or both.

ICH aetiology cannot always be determined when neither a macrovascular cause nor cerebral SVD is detected despite vascular and parenchymal neuroimaging. So-called 'cryptogenic' ICH affects up to 20% of patients[4,16,40]. A 2023 systematic review and meta-analysis of people with ICH of undetermined aetiology, defined as neither structural nor macrovascular causes nor signs of SVD, had a tendency towards higher mortality compared with that of people with identified causes of ICH[16]; however, this finding is likely to be confounded by incomplete diagnostic evaluation owing to early death. Conversely, survivors of cryptogenic ICH with standardized and complete evaluation (including brain MRI) seemed to have a very low rate of recurrent ICH[16]. This finding, together with evidence that an aetiology-based classification system for ICH is associated with a low prevalence of cryptogenic ICH[16], provides another strong argument for complete and structured work-up (including MRI to seek underlying SVD) in most people with ICH to inform prognosis.

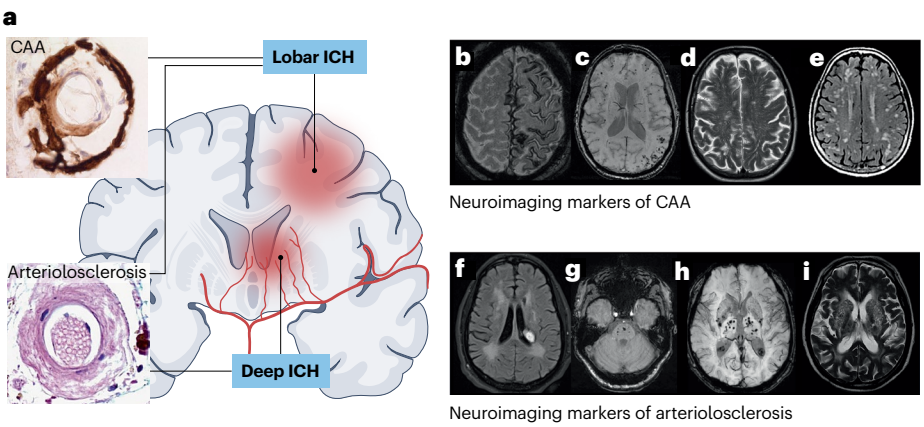

Fig. 1 | Types of cerebral small vessel diseases that cause intracerebral haemorrhage. a, Lobar intracerebral haemorrhage (ICH) is most frequently caused by cerebral amyloid angiopathy (CAA) or arteriolosclerosis. Deep ICH is usually due to arteriolosclerosis. **b**–**i**, Neuroimaging markers of CAA (top row) include cortical superficial siderosis (panel **b**), lobar cerebral microbleeds (panel **c**), enlarged perivascular spaces in the centrum semiovale (panel **d**) and white matter hyperintensities in a multispot pattern (panel **e**). Neuroimaging markers of arteriolosclerosis include deep ICH with periventricular white matter hyperintensities (panel **f**), deep cerebral microbleeds in the pons (panel **g**), deep cerebral microbleeds in the basal ganglia (panel **h**) and severe enlarged perivascular spaces in the basal ganglia (panel **i**).

Box 1 | The DIAGRAM score

The DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study was a prospective, multicentre study that aimed to assess the yield and accuracy of CT angiography, magnetic resonance angiography and digital subtraction catheter angiography in people with non-traumatic intracerebral haemorrhage (ICH) aged 18–70 years (n=298)[27]. In this study, use of digital subtraction catheter angiography was high (52%). On the basis of the study findings, the DIAGRAM score was proposed for assessment of the risk of a macrovascular cause in people with ICH. The DIAGRAM score consists of three variables: age (stratified into categories of 18–50 years and 51–70 years), ICH location (deep, lobar or posterior fossa) and small vessel disease (SVD) changes on CT. The DIAGRAM+ score additionally incorporated CT angiography findings. The highest risk of macrovascular causes was found in people with posterior fossa ICH, younger age, absence of SVD changes on CT and CT angiography leading to suspicion of macrovascular causes. People with deep ICH, higher age and SVD changes on CT had a lower risk of a macrovascular cause.

Genetics and intracerebral haemorrhage

Polymorphisms in several genes are associated with an increased risk of ICH, although such information is not yet widely used in clinical practice. One of the best researched is *APOE*, which encodes apolipoprotein E — a protein involved in lipid metabolism[41]. There are three *APOE* polymorphic alleles[41]: *APOE* ε2 and *APOE* ε4 are less common than *APOE* ε3, but are associated with an increased risk of ICH[41]. Although *APOE* ε4 might be associated with CAA[42], it remains unclear whether this also holds true for *APOE* ε2 (ref. 41). In a post-mortem autopsy study, homozygous or heterozygous carriers of *APOE* ε4 alleles had a higher vascular and parenchymal amyloid load than those who did not carry *APOE* ε4 alleles[42]. In people with Alzheimer disease treated with amyloid-β antibodies, the *APOE* ε4 genotype seemed to be the most important risk factor for amyloid-related imaging abnormalities[43]. Other genetic polymorphisms potentially associated with lobar ICH occur in genes that encode glutathione peroxidase 1, complement C3b/C4b receptor 1, protein kinase Cη (PRKCH) and the integrin αV-subunit, and include variants on locus chr12q21.1 (ref. 44).

Similarly, certain genetic variants on locus 1q22 are associated with white matter hyperintensities in healthy populations and in people with deep ICH[45,46]. Altered regulation of neurotransmitter receptors and blood–brain barrier disruption have been suggested as potential mechanisms[44,45]. Certain polymorphisms in genes that encode COL4A1 and COL4A2, matrix metalloproteinases 2 and 9, TNF and tissue inhibitors of metalloproteinases 1 and 2 might also be associated with deep ICH[44].

The role of monogenetic conditions in young-onset CAA[47] and in SVD[48] have been reviewed elsewhere. Suspicion of a monogenic disease should arise in people under 50 years of age with a positive family history of SVD-related ischaemic stroke or ICH, diffuse white matter hyperintensities and lacunar or subcortical infarcts[49]. The most frequent monogenic SVD is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is caused by mutations in *NOTCH3* (ref. 50). Typically, CADASIL manifests with migraine, subcortical ischaemic stroke, cognitive impairment, neuropsychiatric symptoms and extensive deep SVD with white matter lesions extending into the inferior temporal lobe, but ICH can also occur, although infrequently[50,51]. Other monogenic SVDs that can potentially be associated with ICH include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL; caused by mutations in *HTRA1* with recessive inheritance), pontine autosomal dominant microangiopathy with leukoencephalopathy (PADMAL; caused by mutations in *COL4A1* or *COL4A2* with dominant inheritance) and retinal vasculopathy with cerebral leukodystrophy (caused by *TREX1* mutations)[52]. Hereditary cerebral haemorrhage with amyloidosis is caused by mutations in *APP* on chromosome 21, which encodes the amyloid precursor protein, or mutations in *CST3* on chromosome 20, which encodes cystatin C. Whereas Icelandic-type CAA is found only in some families of Icelandic ancestry, *APP* mutations have been found in Dutch (Dutch-type CAA), Italian and Flemish families, but also in families in Iowa, USA[52]. Interestingly, although people with Down syndrome (characterized by trisomy 21) have a markedly increased risk of Alzheimer disease, which is mainly attributed to the presence of three *APP* genes, their risk of ICH, although elevated compared with that of the general population, is lower than that associated with Dutch-type CAA[53].

Less common SVD subtypes

CAA-related inflammation (CAA-ri) is an entity that arises as an inflammatory response to vascular amyloid deposits[54]. It spans a pathological spectrum from perivascular inflammatory infiltrate to granulomatous angiitis with vessel wall destruction (so-called amyloid-β-related angiitis)[55–57]. In people with neuroimaging evidence of CAA and typical acute symptoms, such as headache, encephalopathy, seizures or focal neurological deficits and asymmetric white matter lesions involving the subcortical white matter, probable CAA-ri can be diagnosed according to proposed neuroimaging CAA-ri criteria[58]. In a comparison of 17 people with autopsy-confirmed CAA-ri and 37 people with non-inflammatory CAA, these criteria demonstrated high specificity (97%) for the diagnosis of CAA-ri. However, the modest sensitivity of 82% and the choice of a control group without typical acute symptoms associated with CAA-ri suggests that CAA-ri might be missed by these criteria in practice[58]. Further research is therefore needed to improve the sensitivity of CAA-ri diagnostic criteria. The risk of CAA-ri recurrence in subsequent years is considerable (around 40% over 2–3 years) even after clinical and radiological stabilization[59,60]. Observational data indicate that early immunosuppression is associated with improved outcomes[60]. Emerging evidence also suggests a role for systemic or cerebrovascular inflammation in the pathogenesis of CAA and Alzheimer disease; however, the extent to which inflammation has a role in the development, pattern or prognosis of ICH in people with CAA in general is unknown[61].

In people with early-onset CAA (before 50 years of age) and a history of human cadaveric growth hormone injection, cadaveric dural graft implantation or other potential exposures to amyloid-β, iatrogenic CAA presumably due to prion-like transmission of amyloid-β should be considered after exclusion of potential concurrent diseases (for example, genetic forms of CAA)[47,62,63]. Iatrogenic CAA seems to manifest clinically 30–40 years after the initial exposure, which is consistent with the pathophysiology of other prion diseases, such as Creutzfeld–Jacob disease or Kuru disease[62]. This long latency has relevance for sporadic CAA, suggesting that amyloid deposition predates clinical symptoms of ICH by many years, and that amyloid-β fibrils propagate within the brain in a similar way to other prions.

Fluid biomarkers in the diagnosis and prognosis of SVD

Several blood biomarkers that are indicative of neuronal damage have been investigated in people with SVD[64]. Neurofilament light chain (NfL) is part of the axonal cytoskeleton[65]. Plasma levels of NfL correlate with the SVD burden, with the presence of SVD markers on MRI, with cognitive decline in people with sporadic SVD or CADASIL[65–67] and with ICH recurrence in people with CAA[68].

Glial fibrillary acidic protein (GFAP) is part of the astrocytic cytoskeleton and can be detected in blood plasma in people with astrocytic damage[69]. Plasma GFAP values were higher in people with ICH than in people with ischaemic stroke in the first few hours following symptom onset[70,71]. Although these studies suggest differences in the pathophysiology of ischaemic stroke and ICH, such blood biomarkers are currently of limited clinical use, as neuroimaging is a faster and more accurate method for disease diagnosis, and because there are currently no approved bedside tests or reliable thresholds for GFAP-based diagnosis in people with a suspected stroke. Both NfL and GFAP values are also associated with incident ICH and ischaemic stroke in people with sporadic and genetic SVD[68,72].

The role of cerebrospinal fluid (CSF) examination in diagnosing the cause of ICH remains uncertain, although some evidence suggests that specific patterns of amyloid-β and tau proteins can help detect CAA. CSF levels of amyloid-β_{42} and amyloid-β_{40} are lower in people with CAA than in healthy controls or people with Alzheimer disease[73], whereas CSF levels of total tau are mildly increased[74]. We recommend obtaining CSF when the imaging diagnosis is uncertain and when confirming the diagnosis of CAA could affect clinical decisions, such as whether to give or withhold antithrombotic treatment.

Current classifications for intracerebral haemorrhage aetiology

Several classification systems exist for non-traumatic ICH. Although stratification according to lobar or non-lobar location is common[75,76], this information alone is insufficient to provide clear insights into disease aetiology, as arteriolosclerosis can cause both deep and lobar ICH, and as CAA and arteriolosclerosis often co-occur[30,38]. Two mechanistic and risk factor-based classifications, SMASH-U[77] and H-ATOMIC[78], were proposed some years ago. SMASH-U attributes ICH to a single aetiology based on a hierarchical algorithm[77], with demonstrated differences in 3-month outcomes according to the assigned cause[4,77]. The H-ATOMIC classification incorporates multiple contributing factors[78], consistent with the high prevalence of multiple vascular risk factors in ICH populations[4].

A comparative analysis found that inter-rater reliability was good for both classifications (SMASH-U, $\kappa = 0.82$; H- ATOMIC, $\kappa = 0.76$)[79]. Nevertheless, these aetiological classifications have considerable limitations: first, they mix causes (for instance, CAA or macrovascular lesions) and risk factors (such as hypertension and anticoagulation)[80,81]. Second, the classifications make assumptions about disease causality; for example, deep ICH location is part of the diagnostic criteria for hypertension-associated ICH, but it can also be caused by macrovascular lesions[77,78].

In the past 2 years, attempts have been made to classify ICH according to direct visualization and categorization of the underlying presence and patterns of SVD biomarkers on neuroimaging; such a classification should preferably be based on findings from MRI[32], but such an approach would be limited in that it cannot be used for people who cannot undergo MRI, for example, due to contraindications, early death or limited resources. The CLAS-ICH classification (Box 2) used clinical and neuroimaging features to define the ICH subtypes arteriolosclerosis, CAA, mixed cerebral SVD, other SVD and secondary causes[29]. Subtypes were classified according to the diagnostic level of certainty, allowing for subtypes to coexist[29]. CLAS-ICH encourages the use of MRI in people with ICH, but also permits the use of CT[29]. The CADMUS classification (Box 2) is an MRI-based classification for ICH associated with sporadic SVD[17]. CADMUS was applied in two independent cohorts of 1,180 and 313 people with ICH with good inter-rater and intra-rater reliability. The major limitation for all classifications to date is the lack of histopathological validation of the underlying SVD. We believe that the classification of ICH aetiology is important, currently under-used and might improve management in the future, comparable with the use of classifications in ischaemic stroke. Future research is needed to show whether CLAS-ICH or CADMUS provide clinical benefit.

Advances and uncertainties in acute therapy

Therapeutic targets

ICH results from the rupture of a blood vessel and bleeding into the brain parenchyma. Although ICH is frequently dichotomized as traumatic versus non-traumatic (spontaneous) ICH, and as 'primary' versus 'secondary to macrovascular causes', an increasing body of evidence indicates that non-traumatic ICH should neither be termed 'spontaneous', owing to the increasing recognition of trigger factors, nor 'primary', owing to the fact that the term is not well defined, and might discourage further investigation, classification or the implementation of rational secondary prevention measures. Beyond underlying vasculopathies, as discussed above, potential trigger factors for vessel rupture in people with ICH can be summarized into two main groups: short-term surges in blood pressure[82,83] and infections[82,84]. Specifically, rapid rises in blood pressure are likely to cause ICH by challenging vessel wall resistance in fragile, small vessels affected by SVD, whereas infection is thought to cause ICH through the induction of endothelial dysfunction and coagulopathy.

At the time of vessel rupture, the ICH causes direct damage to the impacted structures, resulting in the so-called primary or mechanical injury (Fig. 2). In some people, continuous bleeding during the first few hours after ICH onset results in haematoma growth, which

Box 2 | CLAS-ICH and CADMUS

CLAS-ICH[29] is a comprehensive classification that includes five defined intracerebral haemorrhage (ICH) subtypes: arteriosclerosis, cerebral amyloid angiopathy (CAA), mixed small vessel disease (SVD), other rare forms of SVD (that is, genetic SVD) and secondary causes (that is, macrovascular, tumour or rare cause). Patients in each category are scored according to the level of diagnostic evidence (that is, well defined, possible or no evidence).

CADMUS[17] is an MRI-based classification for SVD-related ICH that involves three steps. First, a secondary cause should be excluded. Second, the primary ICH location is scored (deep, lobar or undetermined/cerebellar). Last, haemorrhagic and non-haemorrhagic SVD markers on MRI are scored. Information on the ICH location and the presence or absence of MRI-defined SVD markers is combined to classify patients into one of four mutually exclusive categories: CAA, deep perforator arteriolopathy, mixed CAA (also termed deep perforator arteriopathy) and undetermined SVD.

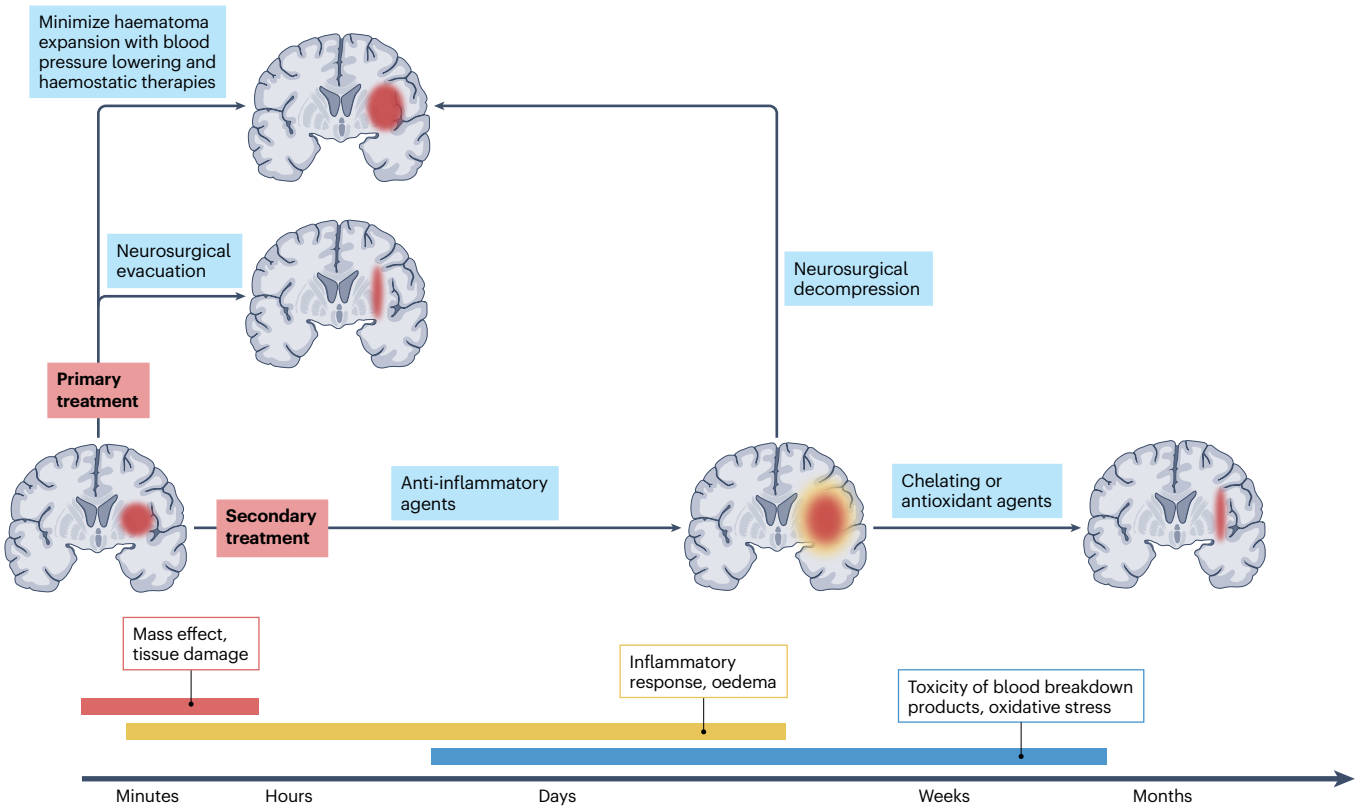

Fig. 2 | Treatment targets and brain damage after intracerebral haemorrhage. Primary treatment in the hyperacute phase of intracerebral haemorrhage (ICH) involves the prevention of secondary haematoma expansion by means of blood pressure lowering and use of haemostatic therapies for patients on therapeutic anticoagulation. Maintaining the haematoma volume as small as possible by preventing haematoma expansion aims to reduce the primary brain damage. Neurosurgical evacuation can also reduce the haematoma volume. Secondary brain damage is mediated by the inflammatory response, oedema, toxicity of blood breakdown products and oxidative stress. Several therapeutic options including anti-inflammatory treatments and decompressive hemicraniectomy might potentially mitigate these effects, but evidence of their efficacy requires validation in randomized controlled trials.

probably occurs in the pre-hospital phase as well as in 20–30% of all patients admitted to hospital[85]. Haematoma expansion is usually captured on repeated imaging[85,86] (Fig. 3), and might involve growth of the main intraparenchymal blood clot itself or new intraventricular extensions[87]. The main predictors of haematoma expansion are time since onset, with the highest risk occurring in the first 3–6 h after symptom onset; baseline haematoma volume, with the highest risk associated with medium to large-sized haematomas; and prior anticoagulation, which is associated with a threefold increased risk of haematoma expansion[86,88]. Time from ICH onset and baseline haematoma volume can be combined to calculate the so-called 'pre-scan haematoma growth rate', which is associated with haematoma expansion and poor outcomes[89,90]. Indeed, haematoma expansion is consistently associated with poor functional outcomes in people with ICH[91] regardless of the definition used (that is, absolute or relative growth). Of note, the studies that support these findings included very few people on oral anticoagulants, in whom the risk of haematoma expansion is increased much further. The process of haematoma growth has been likened to an 'avalanche', where bleeding starts from one primary vessel, which, as the haematoma grows, causes shearing of surrounding 'secondary' vessels, thereby amplifying local bleeding[92]. Findings from a 2022 study suggest that the underlying SVD influences the dynamics of haematoma expansion, with more prolonged and continuous bleeding in people with CAA[93]. Preventing haematoma expansion is a key treatment goal of acute ICH management[85,94] (Fig. 2).

Depending on the size and location of the ICH, intracranial pressure may increase. This pressure might further increase as a consequence of hydrocephalus if the circulation of the CSF is obstructed, often, but not necessarily, owing to intraventricular haemorrhage (IVH). After the 'primary' injury of haematoma expansion and direct tissue injury, the coagulation cascade is initiated[95] together with a pro-inflammatory response in the perihaematomal region[96]. The neurotoxic and pro-inflammatory effects of the extravascular blood are crucially different to the pathophysiologic processes that underlie ischaemic stroke. Components of erythrocytes that have been implicated in the pro-inflammatory response include haemoglobin (and its breakdown products), iron, peroxiredoxin 2 and carbonic anhydrase 1 (ref. 95). Data from animal models, supported by observations in people with ICH, indicate that the pro-inflammatory cascade is activated within hours of haemorrhage and involves the activation of resident microglia and astrocytes, and the infiltration of leucocytes, which propagates neural cell death through processes that involve oxidative stress, and the activation of matrix metalloproteinases and other

proteases, complement proteins and cytokines[96]. This early response is thought to be injurious and abundant, and to evolve over several days following the ICH[96]. Over time, possibly after day 3 (ref. 97), the neuroinflammatory response is thought to change into a 'reparative phase' and become potentially beneficial[96]. Perihaematomal oedema — which is regarded as a radiological marker of secondary injury, including inflammation — typically peaks at day 7–10 after ICH, and is independently associated with poor functional outcomes[98]. Many different factors have a role in the inflammatory response to ICH and knowledge of the exact sequence and consequences of the neuroinflammatory process remains limited. These limitations hinder our ability to understand how detrimental neuroinflammation can be reduced without compromising the beneficial reparative aspects of this process. A 2022 systematic review of molecular markers of inflammation in human brain tissue identified IL-1β as the only marker that was repeatedly upregulated after ICH[99]. A small, randomized trial of a recombinant human IL-1 receptor antagonist showed no harm but also no evidence of an effect on the primary outcome of perihaematomal oedema, although it was not powered for the latter[100]. A phase II trial of the same therapeutic is underway[101].

Accumulating evidence also suggests that, similar to ischaemic stroke, ICH might benefit from early intervention, both in terms of counteracting the primary injury and when directed at reducing the secondary injury[102,103]. However, the optimal timing of the majority of potential treatments remains to be determined.

The care bundle approach and levels of acute care

The management of people with ICH includes different potential treatments targeting a range of mechanisms[94]. Consequently, combining different interventions, including medical and surgical management, under one 'care bundle' umbrella[102] has been increasingly studied[104,105]. In the INTERACT3 trial published in 2023, a care bundle including early intensive blood pressure lowering, glycaemic control, treatment of pyrexia and reversal of anticoagulation improved outcome after ICH[105]. Based on this positive randomized controlled trial and on prior observational data[104], a care bundle approach or 'code ICH' for hyperacute treatment of people with ICH is recommended and promoted by expert panels[100,101].

Pre-hospital triage and ultra-acute management of people with suspected ICH are a further challenge. Neither clinical presentation nor blood-based biomarker tests reliably differentiate ICH from ischaemic stroke[69,106]. Mobile stroke units with CT scanners enable pre-hospital diagnosis of ICH[107,108], which might in turn improve pre-hospital management[109]. The 2024 INTERACT4 trial, which investigated the effect of pre-hospital blood pressure reduction in people with a suspected stroke, found a significant beneficial effect on functional outcome in people with the final diagnosis of ICH[110].

The management of people with ICH is interdisciplinary and might reasonably include specialists from emergency medicine, neurology, neuroradiology, neurosurgery and intensive care. However, not all patients require all levels of care. Stroke unit care improves outcomes after ICH to a similar extent as it does for ischaemic stroke[111]. A 2024 study found that hospital type (that is, primary stroke unit without neurosurgery versus comprehensive stroke centre with neurosurgery) did not influence outcomes after ICH, and neither did secondary transfer from a primary to a comprehensive stroke centre[112]. Indeed, available data suggest that general treatment measures can be delivered even in small, primary stroke units whereas a robust referral pathway should be implemented for patients in need of neurosurgery[113].

Medical treatment for intracerebral haemorrhage

An important goal of acute medical treatment is the prevention of haematoma expansion[85,94]. Limiting secondary brain injury by targeting oedema formation and inflammation is an additional valid goal[100,101] (Fig. 2; see Supplementary Table 1).

Up to 70% of people with ICH have elevated blood pressure at presentation, presumably due to a combination of pre-existing hypertension and the acute response to the ICH[114]. As hypertension is associated with haematoma expansion, perihaematomal oedema and poor outcomes[114], high blood pressure is a plausible treatment target.

Two large, phase III randomized controlled trials investigated the influence of early intensive (INTERACT2) and very intensive (ATACH-II) treatment of elevated blood pressure in people with ICH[115,116] (see Supplementary Table 1). Although neither trial demonstrated a statistically significant beneficial effect of antihypertensive treatment on functional outcome, they nevertheless provided important insights into the

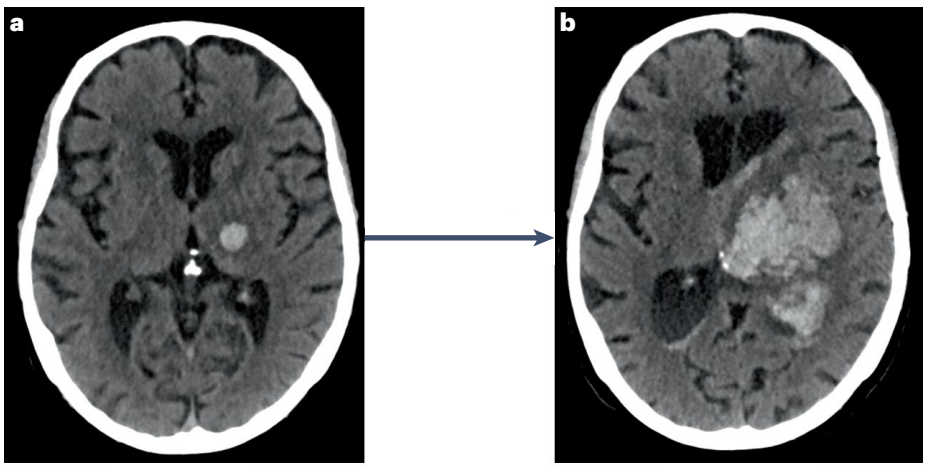

Fig. 3 | Case example of secondary haematoma expansion. A patient on oral anticoagulation therapy with a factor Xa inhibitor (last intake 4 h before) was admitted 45 min after onset of intracerebral haemorrhage (ICH) symptoms. **a**, Baseline CT imaging with a small parenchymal haemorrhage in the left thalamus (1 ml). **b**, Follow-up imaging showed significant haematoma expansion (36.8 ml) and new intraventricular haemorrhage (IVH; 12.5 ml).

effects of acute blood pressure control in people with ICH. Specifically, the trial findings suggested that treatment to a target of <140 mmHg within 1 h of ICH is safe and reduces haematoma expansion[115]. More intensive blood pressure control to a target of 110–139 mmHg caused significantly more renal adverse events, without any benefit on functional outcome[116]. The pooled analysis of individual participant data from these studies showed that achieving early and stable systolic blood pressure control is associated with a 10% increase in the odds of a favourable functional outcome for every 10 mmHg decrease in blood pressure[117]. In a systematic review of 6,221 people from 16 studies of blood pressure reduction in ICH, subgroup analyses suggested that blood pressure interventions are most effective when applied within the first few hours after the onset of symptoms and if titrated to a target blood pressure using α-adrenoreceptor or β-adrenoreceptor blockers[118]. However, neither intravenous magnesium sulfate nor transdermal glyceryl trinitrate administered in an ambulance prior to hospital admission demonstrated beneficial effects in people with ICH[119–121]. By contrast, and as mentioned above, the INTERACT4 trial reported that pre-hospital hyperacute blood pressure lowering to <140 mmHg within 30 min of randomization by administration of urapidil reduced the odds of a poor outcome in people with a final diagnosis of ICH (OR 0.75; 95% CI 0.60–0.92)[110]. The 2022 guidelines of the American Heart Association/American Stroke Association and the 2020 Canadian Stroke Best Practices Recommendations advise lowering of systolic blood pressure in people with ICH within 6 h of symptom onset to a target below 140 mmHg within 1 h of treatment initiation, with the goal of maintaining systolic blood pressure in the range of 130–150 mmHg[122,123], although it must be noted that these guidelines were published before the publication of the most recent trials, including INTERACT4. However, a knowledge gap remains for specific patient groups not included in the trials, including those with large (>30 ml) haematoma volumes, those who present >6 h after ICH onset, those with systolic blood pressure >220 mmHg and those who will undergo surgery. Whether management should differ in ICH subgroups according to the presumed underlying type of SVD[93], whether there is a preferred route of drug administration and the rate at which blood pressure can or should be lowered are also unclear.

People with ICH associated with the use of antithrombotic medications (antiplatelet agents or anticoagulants) have larger baseline haematoma volumes, more haematoma expansion and higher case fatality[88,124,125]. Current guidelines advise that antithrombotic medications are stopped upon hospital admission[126]. In people with ICH who are using antiplatelet therapies, platelet transfusion is associated with a worse functional outcome and should be avoided[127]. It is unclear whether platelet transfusion should be administered to people on antiplatelet therapy for whom surgical evacuation of the haematoma is planned. These uncertainties have led to variations in clinical practice[128]. Of note, a 2023 phase II trial indicated that desmopressin might reduce bleeding in some people with ICH on antiplatelet drugs[129], justifying testing of this agent in a larger randomized trial[129].

Approximately 20% of all ICH cases are associated with prior oral anticoagulant use, with a changing landscape from the use of vitamin K antagonists to direct oral anticoagulants (mainly direct factor Xa inhibitors) during the past few years[130]. Reversal of vitamin K antagonist-associated ICH was studied in the small, randomized controlled INCH trial[131], which found that prothrombin complex concentrate (PCC) was superior to fresh frozen plasma (FFP) in achieving an international normalized ratio <1.3. PCC use was also found to have a lower rate of haematoma expansion; however, the rate of thrombotic complications in the trial overall was high (18%). Moreover, many people with FFP received PCC as rescue therapy during the trial, making it difficult to judge the individual risk of thromboembolic complications associated with each treatment. Evidence from observational studies suggests that early and aggressive reversal of anticoagulation is associated with better outcomes than are slower approaches[132,133]. ICH associated with the use of direct oral anticoagulants can be reversed with PCC or target-specific agents such as andexanet alfa for the oral factor Xa inhibitors[134] and idarucizumab for oral direct thrombin inhibitors[135]. Although no randomized controlled trials have assessed the safety and efficacy of idarucizumab in people with ICH, the randomized, controlled ANNEXA-I trial compared andexanet alfa against usual care (mainly PCC)[136,137], demonstrating a significant benefit of andexanet alfa in haemostatic efficacy, driven by a lower rate of secondary haematoma expansion, but higher rates of thromboembolic events[137]. The trial found no difference in mortality or functional outcome between the two treatments, but was not sufficiently powered to assess this secondary outcome and the functional outcome was assessed early (30 days). A small randomized controlled trial that assessed the antifibrinolytic drug tranexamic acid in patients with direct oral anticoagulant-associated ICH on top of standard of care (PCC) also failed to show any benefit[138]. Indirect comparison between people enrolled in this small trial using non-specific treatments (that is, PCC and/or tranexamic acid) and people enrolled in ANNEXA-4 (ref. 139), a single-arm study in which all participants received andexanet alfa, found a significant reduction in the rate of haematoma expansion in patients receiving andexanet alfa and no difference in the rate of thromboembolic events[140].

In ICH unrelated to prior anticoagulation, several haemostatic agents have been investigated in different doses and time windows, in subgroups with a positive 'spot sign'[141] and within the setting of a mobile stroke unit. Administration of tranexamic acid within 8 h of symptom onset had no significant effect on functional outcome at 90 days but was associated with a reduction in haematoma expansion and early death[142–144]. A small, phase II randomized controlled trial found that tranexamic acid administered in the setting of a mobile stroke unit had no effect on the rate of haematoma expansion or any other clinical outcome[145]. Recombinant activated factor VIIa (rFVIIa) accelerates coagulation by directly activating factor X on the surface of activated platelets. Although most trials with rFVIIa have not shown an effect on functional outcome at 90 days, one trial showed an effect on haematoma expansion[146–148] (see Supplementary Table 1). Ongoing trials are investigating rFVII and tranexamic acid in specific subgroups and earlier (<2–4.5 h) treatment windows (TICH-3 (ref. 149), Indian Trial of Tranexamic Acid[150], TRANSACT[151], Kathmandu tranexamic acid trial[152] and FASTEST[153]). The results of available trials have been summarized in a Cochrane Review[154].

Numerous studies published in the past few years have targeted secondary brain injury, including oedema formation and inflammation, as an approach to improve functional outcomes after ICH. Although used in many places worldwide, mannitol and corticosteroids have no proven benefit on functional outcome and might cause harm[155–157]; randomized trials are therefore required to assess the benefits of these treatments. Two small trials found the matrix metalloproteinase 9 inhibitor, minocycline, to be safe; however, any effect on functional outcome remains to be proven[158,159]. Fingolimod, a sphingosine 1-phosphate receptor modulator, was safe and reduced perihaematomal oedema in a study of 23 people with ICH[160]. By contrast, a phase II trial of the iron

chelator deferoxamine mesylate did not improve clinical outcomes within 90 days of ICH compared with placebo[161].

Ongoing trials are investigating the effects of fingolimod (FITCH[162]; single dose, <24 h), anakinra (ACTION[101]; <8 h for 3 days), atorvastatin (STATIC[163]; <24 h for 7 days), edaravone dexborneol (ED-ICH[162]; <48 h for 14 days) and colchicine (CoVasc-ICH[164]; <48 h), and others are in the planning stages (dimethyl fumarate[165]; <72 h for 3 days), sodium aescinate (REACH[166]; <24 h for 10 days), Chinese herbal medicine FYTF-919 (CHAIN[167]; <48 h), mirabegron[168] (<24 h for 14 days) and celecoxib[169] (<6 h for 21 days).

Early seizures (<7 days) are frequent (3–32%) in people with ICH[170]. Treatment with anti-epileptic medication should be considered after one or more seizures[122,123]. Prophylactic antiseizure medication might be effective in preventing acute seizures, but has not been shown to improve functional outcome so is not recommended[171,172].

Surgical treatment of ICH

As ICH volume is an important predictor of functional outcome, surgical evacuation could theoretically improve outcome by reducing mass effect, lowering intracranial pressure and reducing secondary injuries. However, high-quality randomized clinical trials of craniotomy with evacuation of the haematoma, and of minimally invasive surgery with thrombolysis, have not demonstrated positive outcomes in terms of functional recovery, although these interventions have been associated with reduced mortality, which has been assessed as a secondary outcome[173] (see Supplementary Table 2). As a result, surgical evacuation of ICH is typically performed in a minority of often relatively young patients as a life-saving measure. However, an accumulating body of evidence suggests that surgery with minimally invasive techniques, with or without endoscopy guidance, may in fact improve functional outcome[173]. Outcomes associated with minimally invasive surgery might be better with lower post-treatment volumes[174,175] and earlier treatment might have an advantage over later treatment[173]. However, ultra-early haematoma evacuation by means of craniotomy (within 4 h of symptom onset) was associated with re-bleeding in one study[176], whereas in others early endoscopy-guided surgery seemed to be safe[177,178]. A 2021 study reported a 5% decrease in the odds of achieving good functional outcome at 6 months for each additional hour before evacuation[179]. Of note, assessment of outcomes at 90 days might be too early to capture the full potential for recovery after ICH[180]. The adaptive, randomized ENRICH trial demonstrated that ICH evacuation with minimally invasive trans-sulcal parafascicular surgery improved functional outcomes at 180 days compared with guideline-based medical management — an effect that was mainly driven by outcomes in people with lobar ICH[181]. Although these results are promising, many questions remain, including the generalizability of the results (given that only 2.6% of the 11,603 people who were screened met the inclusion criteria in the ENRICH trial), the preferred surgical technique and the optimal timing of surgical intervention. The results of ongoing randomized controlled trials of different minimally invasive techniques with variable inclusion criteria and in different time windows should shed further light on these questions (see Supplementary Table 2).

The Swiss Trial of Decompressive Craniectomy versus Best Medical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage (SWITCH), which aimed to assess whether decompressive craniectomy could improve outcomes for people with deep ICH[182], was stopped early owing to lack of funding. During the 9 years in which the trial ran, 201 of the target 300 people were randomly assigned to treatment, with available data demonstrating that decompressive craniectomy led to fewer patients with a modified Rankin scale score of 5 or 6, providing weak evidence (adjusted risk ratio 0.77; 95% CI 0.59–1.01; $P = 0.057$) that decompressive craniectomy might be superior to best medical treatment alone. However, the intervention seemed to result in more survivors with a modified Rankin scale score of 4 (moderate severe disability), and no change in the number of people with a modified Rankin scale score of 0–3 (symptom-free to moderately disabled) who were therefore able to return home. Outcomes for decompressive craniectomy are worse for people with ICH than for people with ischaemic stroke[183]. The decision of whether to perform decompressive craniectomy in clinical practice should be strongly informed by the values and ethical beliefs, such as prioritization of survival or autonomy, of individuals being offered the treatment[184].

Surgery for cerebellar haematomas is generally considered in patients with a decreased level of consciousness, brainstem symptoms or when the diameter of the haematoma is ≥3 cm. However, this approach has not been assessed in randomized controlled trials and whether surgery with minimally invasive techniques could improve outcomes is unclear[185].

Advances in prevention measures

Recurrent intracerebral haemorrhage

Assessment of ICH recurrence risk is of high priority for the communication of prognosis to patients and relatives, as well as for physicians who need to make decisions about optimal secondary prevention strategies. People with ICH frequently have conditions associated with a risk of future ischaemic events for which antiplatelet or anticoagulation therapy is usually recommended. Whether to start, resume or discontinue these medications after ICH requires an assessment and balance of the risks of ICH recurrence versus thromboembolic events. Lobar location of ICH is clearly and consistently associated with higher rates of recurrence compared with non-lobar ICH[186–188]. However, this higher risk is probably related to the greater association of lobar ICH with CAA compared with non-lobar forms of ICH, suggesting that consideration of anatomical location may not predict recurrence risk as effectively as consideration of the underlying causal arteriopathy[18]. CAA is the aetiology associated with the highest risk of ICH recurrence, with an estimated recurrence risk of about 7–10% per year[18]. The Boston version 1.5 criteria for probable CAA seem to be more strongly associated with higher ICH recurrence risk than the more recently proposed version 2.0 criteria[189].

In addition to classifying the presumed underlying causal arteriopathy, individual MRI markers of SVD[190] might also have an important role in the assessment of ICH recurrence risk. Perhaps most prominently, cortical superficial siderosis is consistently associated with the most markedly increased risk of recurrent ICH in people with CAA, even after adjusting for the presence and burden of cerebral microbleeds. Nevertheless, larger numbers of cerebral microbleeds also seem to increase the risk of recurrence in people diagnosed with CAA, arteriolosclerosis or both[18]. Small DWI-positive lesions on MRI in the acute stage of the initial ICH might also be associated with a higher ICH recurrence risk, although the data on this association are overall unclear[191,192].

Recurrent ischaemic stroke

The annual risk of ischaemic stroke after ICH is estimated to be 1–4%[3,186,187,193], similar to the annual risk of recurrent ICH. Some studies have reported that the risk of ischaemic stroke is lower after lobar ICH than following non-lobar ICH[186,187] — a difference that might be explained by the lower risk of ischaemic stroke associated with CAA compared

with other causes of ICH[19]. In people with arteriosclerosis-related ICH, the risk of ischaemic stroke seems to be as high as in those with arteriosclerosis-related lacunar stroke[19]. Atrial fibrillation constitutes one of the most important risk factors for recurrent ischaemic stroke in people with ICH[187].

Long-term blood pressure control

As arterial hypertension is the most important risk factor for ICH[194–196], effective blood pressure control is a priority in secondary prevention measures for recurrent ICH. Several trials that have included people with stroke have shown decreased risk of ICH associated with long-term intensive blood pressure control[197,198]. A meta-analysis showed that intensive blood pressure control benefitted people with ICH, associated with a greater reduction in the risk of recurrent vascular events than that achieved in people with ischaemic stroke[199]; however, trials of long-term blood pressure lowering have not been performed specifically in people with ICH. Long-term control of blood pressure is highly relevant in people with arteriolosclerosis and deep ICH as well as in those with lobar ICH[195,200], although specific blood pressure targets have not yet been determined. A large cohort study published in 2023 showed that a systolic blood pressure target of <120 mmHg decreased the risk of recurrent ICH and other vascular events in people with prior ICH[200].

The ongoing multinational, randomized TRIDENT study will investigate the effect of a triple-combination antihypertensive blood pressure pill (comprising telmisartan, amlodipine and indapamide) in addition to standard care to reduce recurrent stroke after ICH[201]. The PROHIBIT-ICH study[202] compared a strategy of intensive blood pressure management (target <120/80 mmHg) guided by telemetric home monitoring with standard care to assess the feasibility of this approach and its influence on MRI outcome measures including white matter hyperintensity volume; the trial has been completed and publication of the results is awaited.

Antiplatelet and anticoagulation therapy after intracerebral haemorrhage

The safety of antithrombotic therapy has long been questioned and the initiation of such therapies has traditionally been avoided after ICH out of concern for increasing the risk of recurrent ICH. The RESTART[203] open-label pilot randomized controlled trial found no signal of harm if antiplatelet agents were restarted in people who had previously taken antithrombotic therapy for the prevention of occlusive vascular disease, a median of 76 days from the onset of ICH symptoms. Moreover, people who reinitiated antiplatelet therapy experienced numerically fewer ICH recurrences than those who did not restart therapy (adjusted hazard ratio 0.51; 95% CI 0.25–1.03; $P = 0.06$). The results were consistent across subgroups including those stratified by ICH location, time since symptom onset, type of antiplatelet drug, participant age and history of atrial fibrillation. Extended follow-up for up to 7 years found no significant effect of antiplatelet therapy on ICH recurrence or vascular events[204]. Moreover, a brain imaging sub-study of the RESTART trial ($n = 254$ with MRI)[205] found that initiation of antiplatelet therapy did not lead to an increase of recurrent ICH in people with high-risk features, such as cerebral microbleeds or fulfilling the diagnostic criteria for CAA. These findings reassure physicians about the safety of using antiplatelet drugs in people who have had an ICH, although whether this strategy is beneficial remains unclear. Further randomized controlled trials aim to address this question, including ASPIRING[206].

Observational studies of anticoagulant therapy reinitiated after ICH in people with atrial fibrillation have demonstrated a reduction in the risk of ischaemic stroke, without an increased risk of ICH recurrence[132,207]. However, treatment biases and confounding might have influenced these studies. More recent results from two small randomized controlled trials (SoSTART and APACHE-AF) indicate that anticoagulant therapy in people with atrial fibrillation and a history of ICH increased the risk of recurrent ICH but tended to lower the rates of recurrent ischaemic stroke; however, the study samples were too small to draw clear conclusions about safety or efficacy[208,209]. An individual patient data analysis (COCROACH[210]) found a significant reduction in the rate of thromboembolic events in people with atrial fibrillation using oral anticoagulants (mainly direct oral anticoagulants) after ICH compared with those not using anticoagulants, along with a non-significant increase in major haemorrhagic events. However, the study was not powered to provide a definite answer on the safety and efficacy of this intervention. Ongoing trials will provide crucial insights in the coming years (see Supplementary Table 3).

Certain subgroups of people with ICH (those at low risk of recurrent ICH and at high risk of cardioembolism) might be thought to benefit from anticoagulation, whereas those at very high risk of recurrent ICH, such as people with severe CAA (manifested as disseminated cortical superficial siderosis, previous multiple recurrences or both) might be harmed. The data safety and monitoring committee of ENRICH-AF recommended that the enrolment of people with lobar ICH and convexity subarachnoid haemorrhage — both considered to be mainly caused by CAA — was stopped owing to the unexpected high rate of recurrent ICH in participants assigned to receive edoxaban[211]. However, no such observation was made in the smaller completed trials, and some other ongoing trials continue to enrol this patient group. In the absence of definite evidence from randomized controlled trials, we suggest a potential approach to these decisions (Fig. 4).

Utility of left atrial appendage occlusion

Approximately 80% of all thrombi in the left atrium form in the left atrial appendage[212]. Therefore, surgical or percutaneous occlusion (left atrial appendage occlusion (LAAO)) is an appealing option for people with ICH and concomitant atrial fibrillation as it does not require long-term anticoagulation. Evidence of the efficacy and safety of this approach is derived from three randomized controlled trials in people with high bleeding risk, which compared LAAO with warfarin (in two studies) or direct oral anticoagulants (in one study)[213–215]. However, randomized data of people with ICH and atrial fibrillation are lacking. Four small cohort studies (two in people with CAA and two in people with unselected ICH) reported that LAAO had a good safety profile[216,217]. Relevant ongoing trials include the A3ICH study[218], which aims to compare anticoagulation, LAAO or no such therapy in people with ICH, and the STROKE-CLOSE study[219], which aims to compare LAAO with medical therapy in people with ICH. Further studies include ASAP-TOO[220], CLOSURE-AF[165] and COMPARE-LAAO[221], which aim to investigate LAAO in people with atrial fibrillation and contraindications to anticoagulation or at high risk of haemorrhage.

Statins and other lipid-lowering drugs

Dyslipidaemia is an important risk factor for vascular disease and present in a considerable proportion of people with ICH[222,223]. However, the use of statins in people with ICH has been controversial. Early studies of statins in people with prior stroke showed a decreased risk of vascular events; however, subgroup analyses indicated an increased risk

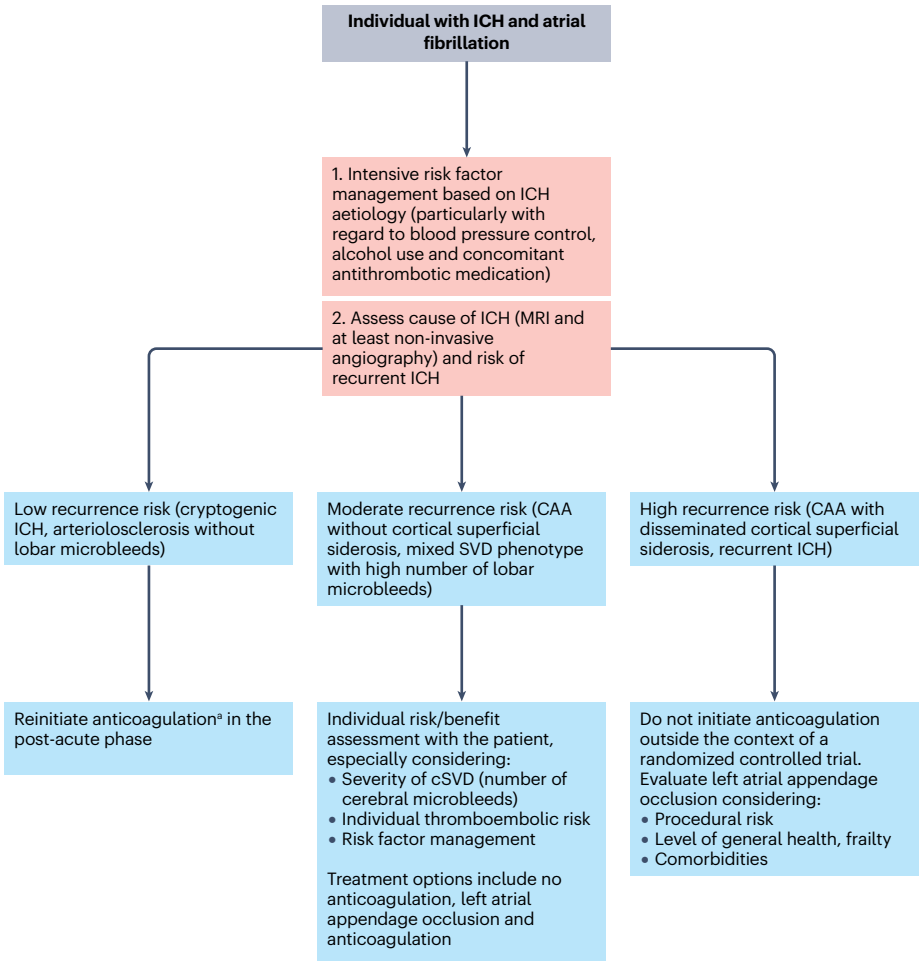
Individual with ICH and atrial fibrillation
1. Intensive risk factor management based on ICH aetiology (particularly with regard to blood pressure control, alcohol use and concomitant antithrombotic medication)
2. Assess cause of ICH (MRI and at least non-invasive angiography) and risk of recurrent ICH
Low recurrence risk (cryptogenic ICH, arteriolosclerosis without lobar microbleeds)
Moderate recurrence risk (CAA without cortical superficial siderosis, mixed SVD phenotype with high number of lobar microbleeds)
High recurrence risk (CAA with disseminated cortical superficial siderosis, recurrent ICH)
Reinitiate anticoagulation[a] in the post-acute phase
Individual risk/benefit assessment with the patient, especially considering:
• Severity of cSVD (number of cerebral microbleeds)
• Individual thromboembolic risk
• Risk factor management
Treatment options include no anticoagulation, left atrial appendage occlusion and anticoagulation
Do not initiate anticoagulation outside the context of a randomized controlled trial. Evaluate left atrial appendage occlusion considering:
• Procedural risk
• Level of general health, frailty
• Comorbidities

Fig. 4 | Algorithm for deciding whether to initiate or resume oral anticoagulation and other treatment options in people with intracerebral haemorrhage and atrial fibrillation. A notable number of people with intracerebral haemorrhage (ICH) have concomitant atrial fibrillation. Key factors in the decision to initiate or resume oral anticoagulation in this group include the risk of ICH recurrence on the basis of ICH aetiology, the severity of underlying cerebral small vessel disease (SVD), the risk of cardioembolism, and factors and wishes that are important to each individual. CAA, cerebral amyloid angiopathy. [a]Anticoagulation with a direct oral anticoagulant (DOAC) is recommended owing to the lower risk of intracranial haemorrhage for these agents compared with vitamin K antagonists.

of haemorrhagic stroke in survivors of ICH[224,225]. Statins may inhibit platelet function, have pro-fibrinolytic capacities and decrease the expression of tissue factor, thereby attenuating the generation of thrombin[226–228]. Furthermore, observational studies identified a higher risk of ICH in people with low levels of LDL and total cholesterol[229–233]. Conversely, a large meta-analysis of statin trials showed no increased risk of recurrent ICH in people with previous ICH who were taking statins[234]. A large regional case–control registry study indicated that statin use was actually associated with a lower risk of ICH[235]. Although one randomized controlled trial showed no difference in the risk of ICH associated with different LDL target levels in people with ischaemic stroke[236], no prospective randomized controlled trials have been performed in people with ICH. The ongoing Statins in Intracerebral Hemorrhage (SATURN[237]) trial, which will randomly assign people with ICH and prior statin therapy to continuation or discontinuation of therapy, will likely shed more light on this relevant issue.

No association has been found between PCSK9 inhibitor use and long-term risk of intracranial haemorrhage[238], indicating the potential utility of these agents in people with a history of ICH. However, this observation is again limited by a lack of data from people with ICH, and even more so by the exclusion of those people from large trials of PCSK9 inhibitors, limiting our ability to draw any clear conclusions about their use in this patient population.

Disease-modifying therapies in cerebral small vessel diseases

Despite the massive impact of arteriolosclerosis and CAA, not limited to a cause of ICH but also their pathogenic role in dementia and other non-motor symptoms, no disease-specific treatment options exist in clinical practice beyond risk factor management. As discussed above, intensive blood pressure management is currently the primary long-term treatment option to slow the progression of SVD, including arteriolosclerosis. A subgroup of participants from the SPRINT trial who underwent MRI reported a slightly smaller increase of white matter hyperintensities in those who were randomly assigned to the intensive blood pressure-control group (target <120 mmHg) than those assigned to standard blood pressure control[239]. However, the PRESERVE trial, which specifically targeted people with arteriolosclerosis, did not show such an effect[58]. Two meta-analyses of randomized trials that assessed the effects of antihypertensive medications on markers of cerebral SVD showed that the progression of white matter hyperintensities was reduced in people under (intensive) antihypertensive treatment compared with that of people who received standard blood pressure control[239,240].

The LACI-2 trial showed that isosorbide mononitrate or combination treatment with isosorbide mononitrate and cilostazol — which have both demonstrated beneficial effects on small vessel endothelium in experimental studies — decreased the risk of recurrent stroke and cognitive impairment among people who had experienced lacunar

stroke[241]. Although people with ICH were not included in that study, the results indicate the need for further studies that particularly target people with arteriolosclerosis-related ICH. The updated 2023 Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)-2 criteria[190] and the Framework for Clinical Trials in Cerebral Small Vessel Disease (FINESSE)[242] will further guide research on SVD-related neuroimaging findings.

No disease-modifying treatment currently exists for CAA. Multiple potential therapy targets are currently in development or under evaluation, including anti-amyloid antibodies and other compounds to remove amyloid-β plaques[243] and soluble amyloid-β[244] or to reduce the production of amyloid-β[245,246]. A trial of an intrathecal RNA interference molecule to reduce expression of the *APP* gene, and therefore amyloid-β production and vascular deposition, is underway[247]. Beyond amyloid-targeted treatments, the fibrinolytic system might be another potential treatment target[248]. Minocycline inhibits the degradation of perivascular extracellular matrix in cerebral small vessels[249]. A 2024 study suggested that minocycline is safe, generally well tolerated and associated with reduced ICH recurrence in a small group of people with clinically aggressive CAA[250]. Future treatment options in CAA might include anti-inflammatory therapies if inflammatory activity is found to be clinically relevant for intracranial bleeding in CAA.

Conclusions and future directions

Although ICH remains a major challenge for patients, families, carers and healthcare providers, advances in our understanding of the drivers of morbidity and mortality and the identification of potential treatment options provide optimism that improved outcomes might finally be possible. Recognition of the underlying aetiologies, effects of specific acute medical and surgical treatments, as well as new data relevant to the secondary prevention of major adverse vascular events should all contribute to better treatments for ICH. Organization of care including pre-hospital triage and management, hospital level of care and use of integrated care pathways (such as care bundles, and the 'code ICH' approach) are currently major implementation challenges. Alongside the recent surge in promising randomized controlled trials, future interventional studies based on improved understanding of ICH disease mechanisms and natural history should help answer many key clinical questions and improve outcomes for people with ICH.

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References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* **20**, 795–820 (2021).
2. van Asch, C. J. et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol.* **9**, 167–176 (2010).
3. Poon, M. T., Fonville, A. F. & Al-Shahi Salman, R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* **85**, 660–667 (2014).
4. Goeldlin, M. B. et al. Etiology, 3-month functional outcome and recurrent events in non-traumatic intracerebral hemorrhage. *J. Stroke* **24**, 266–277 (2022).
5. Foster, L. et al. Effect of deferoxamine on trajectory of recovery after intracerebral hemorrhage: a post hoc analysis of the i-DEF trial. *Stroke* https://doi.org/10.1161/strokeaha.121.037298 (2022).
6. Shah, V. A. et al. One-year outcome trajectories and factors associated with functional recovery among survivors of intracerebral and intraventricular hemorrhage with initial severe disability. *JAMA Neurol.* **79**, 856–868 (2022).
7. Ozkan, H. et al. Prevalence, patterns, and predictors of patient-reported non-motor outcomes at 30 days after acute stroke: prospective observational hospital cohort study. *Int. J. Stroke* https://doi.org/10.1177/17474930231215660 (2023).
8. Pasi, M. et al. Long-term functional decline of spontaneous intracerebral haemorrhage survivors. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2020-324741 (2020).
9. Scopelliti, G. et al. Long-term anxiety in spontaneous intracerebral hemorrhage survivors. *Int. J. Stroke* **17**, 1093–1099 (2022).
10. Scopelliti, G. et al. Fatigue after spontaneous intracerebral haemorrhage: prevalence and associated factors. *Neurological Sci.* **15**, 2127–2135 (2023).
11. Moulin, S. et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *Lancet Neurol.* **15**, 820–829 (2016).
12. Tilling, E. J., El Tawil, S. & Muir, K. W. Do clinicians overestimate the severity of intracerebral hemorrhage? *Stroke* https://doi.org/10.1161/strokeaha.118.022606 (2019).
13. Samarasekera, N. et al. Influence of intracerebral hemorrhage location on incidence, characteristics, and outcome: population-based study. *Stroke* **46**, 361–368 (2015).
14. Tamborska, A., Poon, M. T. C. & Al-Shahi Salman, R. Characteristics of randomized trials focusing on stroke due to intracerebral hemorrhage: systematic review. *Stroke* **49**, 594–600 (2018).
15. Hostettler, I. C., Seiffge, D. J. & Werring, D. J. Intracerebral hemorrhage: an update on diagnosis and treatment. *Expert. Rev. Neurother.* **19**, 679–694 (2019).
16. Fandler-Höfler, S. et al. Association of the presence and pattern of MRI markers of cerebral small vessel disease with recurrent intracerebral hemorrhage. *Neurology* **101**, e794–e804 (2023).
17. Goeldlin, M. B. et al. CADMUS. *Neurology* **102**, e207977 (2024).
18. Charidimou, A. et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: a meta-analysis. *Neurology* **89**, 820–829 (2017).
19. Goeldlin, M. B. et al. Small vessel disease burden and risk of recurrent cerebrovascular events in patients with lacunar stroke and intracerebral haemorrhage attributable to deep perforator arteriolopathy. *Eur. Stroke J.* https://doi.org/10.1177/23969873231193237 (2023).
20. Bekelis, K. et al. Computed tomography angiography: improving diagnostic yield and cost effectiveness in the initial evaluation of spontaneous nonsubarachnoid intracerebral hemorrhage. *J. Neurosurg.* **117**, 761–766 (2012).
21. Delgado Almandoz, J. E. et al. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *AJNR Am. J. Neuroradiol.* **30**, 1213–1221 (2009).
22. van Asch, C. J. et al. External validation of the secondary intracerebral hemorrhage score in The Netherlands. *Stroke* **44**, 2904–2906 (2013).
23. Cordonnier, C., Klijn, C. J., van Beijnum, J. & Al-Shahi Salman, R. Radiological investigation of spontaneous intracerebral hemorrhage: systematic review and trinational survey. *Stroke* **41**, 685–690 (2010).
24. van Asch, C. J. et al. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ* **351**, h5762 (2015).
25. Dawkins, A. A. et al. Complications of cerebral angiography: a prospective analysis of 2,924 consecutive procedures. *Neuroradiology* **49**, 753–759 (2007).
26. Kaufmann, T. J. et al. Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients. *Radiology* **243**, 812–819 (2007).
27. Hilkens, N. A. et al. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. *J. Neurol. Neurosurg. Psychiatry* **89**, 674–679 (2018).
28. Fandler-Höfler, S. et al. MRI-based prediction of macrovascular causes of intracerebral hemorrhage: the MACRO score. *Neurology* **103**, e209950 (2024).
29. Raposo, N. et al. A causal classification system for intracerebral hemorrhage subtypes. *Ann. Neurol.* **93**, 16–28 (2023).
30. Rodrigues, M. A. et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol.* **17**, 232–240 (2018).
31. Fandler-Hofler, A. S. S. et al. Association of presence and pattern of MRI markers of cerebral small vessel disease with recurrent intracerebral hemorrhage. *Neurology* **101**, e794–e804 (2023).
32. Goeldlin, M. et al. Clinical neuroimaging in intracerebral haemorrhage related to cerebral small vessel disease: contemporary practice and emerging concepts. *Expert. Rev. Neurother.* **22**, 579–594 (2022).
33. Greenberg, S. M. & Vonsattel, J. P. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. *Stroke* **28**, 1418–1422 (1997).
34. Jäkel, L., De Kort, A. M., Klijn, C. J. M., Schreuder, F. & Verbeek, M. M. Prevalence of cerebral amyloid angiopathy: a systematic review and meta-analysis. *Alzheimer's Dement.* **18**, 10–28 (2022).
35. Charidimou, A. et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol.* **21**, 714–725 (2022).
36. Linn, J. et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* **74**, 1346–1350 (2010).
37. Perosa, V. et al. Histopathological correlates of lobar microbleeds in false-positive cerebral amyloid angiopathy cases. *Ann. Neurol.* **94**, 856–870 (2023).
38. Pasi, M. et al. Mixed-location cerebral hemorrhage/microbleeds: underlying microangiopathy and recurrence risk. *Neurology* **90**, e119–e126 (2018).
39. Jolink, W. M. T. et al. Histopathology of cerebral microinfarcts and microbleeds in spontaneous intracerebral hemorrhage. *Transl. stroke Res.* **14**, 174–184 (2023).
40. Malhotra, K. et al. Prevalence, characteristics, and outcomes of undetermined intracerebral hemorrhage: a systematic review and meta-analysis. *Stroke* **52**, 3602–3612 (2021).

41. Falcone, G. J. & Woo, D. Genetics of spontaneous intracerebral hemorrhage. *Stroke* https://doi.org/10.1161/strokeaha.117.017072 (2017).
42. Caselli, R. J., Walker, D., Sue, L., Sabbagh, M. & Beach, T. Amyloid load in nondemented brains correlates with APOE ε4. *Neurosci. Lett.* **473**, 168–171 (2010).
43. Filippi, M. et al. Amyloid-related imaging abnormalities and β-amyloid-targeting antibodies: a systematic review. *JAMA Neurol.* **79**, 291–304 (2022).
44. Guo, H. et al. Genetics of spontaneous intracerebral hemorrhage: risk and outcome. *Front. Neurosci.* **16**, 874962 (2022).
45. Woo, D. et al. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am. J. Hum. Genet.* **94**, 511–521 (2014).
46. Fornage, M. et al. Genome-wide association studies of cerebral white matter lesion burden: the CHARGE consortium. *Ann. Neurol.* **69**, 928–939 (2011).
47. Banerjee, G. et al. Clinical considerations in early-onset cerebral amyloid angiopathy. *Brain.* **146**, 3991–4014 (2023).
48. Manini, A. & Pantoni, L. Genetic causes of cerebral small vessel diseases: a practical guide for neurologists. *Neurology* **100**, 766–783 (2023).
49. Yamamoto, Y., Craggs, L., Baumann, M., Kalimo, H. & Kalaria, R. N. Review: molecular genetics and pathology of hereditary small vessel diseases of the brain. *Neuropathol. Appl. Neurobiol.* **37**, 94–113 (2011).
50. Bersano, A. et al. The role of clinical and neuroimaging features in the diagnosis of CADASIL. *J. Neurol.* **265**, 2934–2943 (2018).
51. Liao, Y. C. et al. Intracerebral hemorrhage in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: prevalence, clinical and neuroimaging features and risk factors. *Stroke* https://doi.org/10.1161/strokeaha.120.030664 (2021).
52. Sondergaard, C. B., Nielsen, J. E., Hansen, C. K. & Christensen, H. Hereditary cerebral small vessel disease and stroke. *Clin. Neurol. Neurosurg.* **155**, 45–57 (2017).
53. Buss, L. et al. Intracerebral haemorrhage in Down syndrome: protected or predisposed? *F1000Res* **5**, https://doi.org/10.12688/f1000research.7819.1 (2016).
54. Kozberg, M. G., Perosa, V., Gurol, M. E. & van Veluw, S. J. A practical approach to the management of cerebral amyloid angiopathy. *Int. J. Stroke* **16**, 356–369 (2021).
55. Chu, S., Xu, F., Su, Y., Chen, H. & Cheng, X. Cerebral amyloid angiopathy (CAA)-related inflammation: comparison of inflammatory CAA and amyloid-β-related angiitis. *J. Alzheimers Dis.* **51**, 525–532 (2016).
56. Salvarani, C. et al. Aβ-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* **81**, 1596–1603 (2013).
57. Scolding, N. J. et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* **128**, 500–515 (2005).
58. Auriel, E. et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol.* **73**, 197–202 (2016).
59. Antolini, L. et al. Spontaneous ARIA-like events in cerebral amyloid angiopathy-related inflammation: a multicenter prospective longitudinal cohort study. *Neurology* **97**, e1809–e1822 (2021).
60. Regenhardt, R. W. et al. Association between immunosuppressive treatment and outcomes of cerebral amyloid angiopathy-related inflammation. *JAMA Neurol.* **77**, 1261–1269 (2020).
61. Low, A., Mak, E., Rowe, J. B., Markus, H. S. & O'Brien, J. T. Inflammation and cerebral small vessel disease: a systematic review. *Ageing Res. Rev.* **53**, 100916 (2019).
62. Banerjee, G. et al. Iatrogenic cerebral amyloid angiopathy: an emerging clinical phenomenon. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2022-328792 (2022).
63. Kaushik, K. et al. Iatrogenic cerebral amyloid angiopathy post neurosurgery: frequency, clinical profile, radiological features, and outcome. *Stroke* **54**, 1214–1223 (2023).
64. Khalil, M. et al. Neurofilaments as biomarkers in neurological disorders. *Nat. Rev. Neurol.* **14**, 577–589 (2018).
65. Qu, Y. et al. Association of plasma neurofilament light with small vessel disease burden in nondemented elderly: a longitudinal study. *Stroke* **52**, 896–904 (2021).
66. Duering, M. et al. Serum neurofilament light chain levels are related to small vessel disease burden. *J. Stroke* **20**, 228–238 (2018).
67. Egle, M. et al. Neurofilament light chain predicts future dementia risk in cerebral small vessel disease. *J. Neurol. Neurosurg. Psychiatry* **92**, 582–589 (2021).
68. Cheng, X. et al. Neurofilament light chain predicts risk of recurrence in cerebral amyloid angiopathy-related intracerebral hemorrhage. *Aging* **12**, 23727–23738 (2020).
69. Perry, L. A. et al. Glial fibrillary acidic protein for the early diagnosis of intracerebral hemorrhage: systematic review and meta-analysis of diagnostic test accuracy. *Int. J. Stroke* **14**, 390–399 (2019).
70. Katsanos, A. H. et al. Plasma glial fibrillary acidic protein in the differential diagnosis of intracerebral hemorrhage. *Stroke* **48**, 2586–2588 (2017).
71. Luger, S. et al. Diagnostic accuracy of glial fibrillary acidic protein and ubiquitin carboxy-terminal hydrolase-L1 serum concentrations for differentiating acute intracerebral hemorrhage from ischemic stroke. *Neurocrit. Care* **33**, 39–48 (2020).
72. Chen, C. H., Cheng, Y. W., Chen, Y. F., Tang, S. C. & Jeng, J. S. Plasma neurofilament light chain and glial fibrillary acidic protein predict stroke in CADASIL. *J. Neuroinflammation* **17**, 124 (2020).
73. Verbeek, M. M. et al. Cerebrospinal fluid amyloid β_{40} is decreased in cerebral amyloid angiopathy. *Ann. Neurol.* **66**, 245–249 (2009).
74. Renard, D. et al. Interest of CSF biomarker analysis in possible cerebral amyloid angiopathy cases defined by the modified Boston criteria. *J. Neurol.* **259**, 2429–2433 (2012).
75. Smith, E. E. et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke* **41**, 1933–1938 (2010).
76. Charidimou, A. et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): development and assessment of reliability. *J. Neurol. Sci.* **372**, 178–183 (2017).
77. Meretoja, A. et al. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. *Stroke* **43**, 2592–2597 (2012).
78. Marti-Fabregas, J. et al. The H-ATOMIC criteria for the etiologic classification of patients with intracerebral hemorrhage. *PLoS ONE* **11**, e0156992 (2016).
79. Marti-Fabregas, J. et al. SMASH-U versus H-ATOMIC: a head-to-head comparison for the etiologic classification of intracerebral hemorrhage. *J. Stroke Cerebrovasc. Dis.* **27**, 2375–2380 (2018).
80. Jackson, C. A. & Sudlow, C. L. Is hypertension a more frequent risk factor for deep than for lobar supratentorial intracerebral haemorrhage? *J. Neurol. Neurosurg. Psychiatry* **77**, 1244–1252 (2006).
81. Seiffge, D. J. et al. Small vessel disease burden and intracerebral haemorrhage in patients taking oral anticoagulants. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2020-325299 (2021).
82. van Etten, E. S. et al. Trigger factors for spontaneous intracerebral hemorrhage: a case-crossover study. *Stroke* **53**, 1692–1699 (2022).
83. Sallinen, H., Putaala, J. & Strbian, D. Triggering factors in non-traumatic intracerebral hemorrhage. *J. Stroke Cerebrovasc. Dis.* **29**, 104921 (2020).
84. Elkind, M. S. V., Boehme, A. K., Smith, C. J., Meisel, A. & Buckwalter, M. S. Infection as a stroke risk factor and determinant of outcome after stroke. *Stroke* **51**, 3156–3168 (2020).
85. Morotti, A. et al. Intracerebral haemorrhage expansion: definitions, predictors, and prevention. *Lancet Neurol.* **22**, 159–171 (2023).
86. Al-Shahi Salman, R. et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol.* **17**, 885–894 (2018).
87. Yogendrakumar, V. et al. Redefining hematoma expansion with the inclusion of intraventricular hemorrhage growth. *Stroke* **51**, 1120–1127 (2020).
88. Seiffge, D. J. et al. Meta-analysis of haematoma volume, haematoma expansion and mortality in intracerebral haemorrhage associated with oral anticoagulant use. *J. Neurol.* **266**, 3126–3135 (2019).
89. Rodriguez-Luna, D. et al. Ultraearly hematoma growth in active intracerebral hemorrhage. *Neurology* **87**, 357–364 (2016).
90. Rodriguez-Luna, D. et al. Ultraearly hematoma growth predicts poor outcome after acute intracerebral hemorrhage. *Neurology* **77**, 1599–1604 (2011).
91. Dowlatshahi, D. et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. *Neurology* **76**, 1238–1244 (2011).
92. Schlunk, F. & Greenberg, S. M. The pathophysiology of intracerebral hemorrhage formation and expansion. *Transl. stroke Res.* **6**, 257–263 (2015).
93. Seiffge, D. J. et al. Cerebral amyloid angiopathy and the risk of hematoma expansion. *Ann. Neurol.* **92**, 921–930 (2022).
94. Seiffge, D. J. & Anderson, C. S. Treatment for intracerebral hemorrhage: dawn of a new era. *Int. J. Stroke* **19**, 482–489 (2024).
95. Xia, F. et al. The fate of erythrocytes after cerebral hemorrhage. *Transl. Stroke Res.* **13**, 655–664 (2022).
96. Xue, M. & Yong, V. W. Neuroinflammation in intracerebral haemorrhage: immunotherapies with potential for translation. *Lancet Neurol.* **19**, 1023–1032 (2020).
97. Ohashi, S. N. et al. Role of inflammatory processes in hemorrhagic stroke. *Stroke* **54**, 605–619 (2023).
98. Cliteur, M. P. et al. The association between perihaematomal oedema and functional outcome after spontaneous intracerebral haemorrhage: a systematic review and meta-analysis. *Eur. Stroke J.* **8**, 423–433 (2023).
99. Loan, J. J. et al. Secondary injury and inflammation after intracerebral haemorrhage: a systematic review and meta-analysis of molecular markers in patient brain tissue. *J. Neurol. Neurosurg. Psychiatry* **93**, 126–132 (2022).
100. Parry-Jones, A. R. et al. Phase II randomised, placebo-controlled, clinical trial of interleukin-1 receptor antagonist in intracerebral haemorrhage: BLOcking the Cytokine IL-1 in ICH (BLOC-ICH). *Eur. Stroke J.* **8**, 819–827 (2023).
101. Cliteur, M. P. et al. Anakinra in cerebral haemorrhage to target secondary injury resulting from neuroinflammation (ACTION): study protocol of a phase II randomised clinical trial. *Eur. Stroke J.* **9**, 265–273 (2024).
102. Parry-Jones, A. R. et al. Acute care bundles should be used for patients with intracerebral haemorrhage: an expert consensus statement. Eur. Stroke J. https://doi.org/10.1177/23969873231220235 (2023).
103. Li, Q. et al. Code ICH: a call to action. *Stroke* **55**, 494–505 (2023).
104. Parry-Jones, A. R. et al. An intracerebral hemorrhage care bundle is associated with lower case fatality. *Ann. Neurol.* **86**, 495–503 (2019).
105. Ma, L. et al. The third intensive care bundle with blood pressure reduction in acute cerebral haemorrhage trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. *Lancet* **402**, 27–40 (2023).
106. Luger, S. et al. Glial fibrillary acidic protein serum levels distinguish between intracerebral hemorrhage and cerebral ischemia in the early phase of stroke. *Clin. Chem.* **63**, 377–385 (2017).
107. Cooley, S. R. et al. Mobile stroke units facilitate prehospital management of intracerebral hemorrhage. *Stroke* **52**, 3163–3166 (2021).

108. Walter, S. et al. European Stroke Organisation (ESO) guidelines on mobile stroke units for prehospital stroke management. *Eur. Stroke J.* **7**, xxvii–lix (2022).
109. Schwabauer, E. et al. Effects of Mobile Stroke Unit dispatch on blood pressure management and outcomes in patients with intracerebral haematoma: results from the Berlin_Prehospital Or Usual Care Delivery in acute Stroke (B_PROUD) controlled intervention study. *Eur. Stroke J.* **9**, 366–375 (2024).
110. Li, G. et al. Intensive ambulance-delivered blood-pressure reduction in hyperacute stroke. *N. Engl. J. Med.* **390**, 1862–1872 (2024).
111. Langhorne, P. et al. Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. *Stroke* **44**, 3044–3049 (2013).
112. Marti-Fabregas, J. et al. Influence of hospital type on outcomes of patients with acute spontaneous intracerebral hemorrhage: a population-based study. *Neurology* **103**, e209539 (2024).
113. Seiffge, D. J. Good treatment of hyperacute intracerebral hemorrhage is as easy as ABC. *Neurology* **103**, e209614 (2024).
114. Willmot, M., Leonardi-Bee, J. & Bath, P. M. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* **43**, 18–24 (2004).
115. Anderson, C. S. et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N. Engl. J. Med.* **368**, 2355–2365 (2013).
116. Qureshi, A. I. et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N. Engl. J. Med.* **375**, 1033–1043 (2016).
117. Moullaali, T. J. et al. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. *Lancet Neurol.* **18**, 857–864 (2019).
118. Moullaali, T. J. et al. Early lowering of blood pressure after acute intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *J. Neurol. Neurosurg. Psychiatry* **93**, 6–13 (2022).
119. Saver, J. L. et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N. Engl. J. Med.* **372**, 528–536 (2015).
120. van den Berg, S. A. et al. Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial. *Lancet Neurol.* **21**, 971–981 (2022).
121. Investigators, R.- Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet* **393**, 1009–1020 (2019).
122. Greenberg, S. M. et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke* **53**, e282–e361 (2022).
123. Shoamanesh, A. et al. Canadian stroke best practice recommendations: management of spontaneous intracerebral hemorrhage, 7th edition update 2020. *Int. J. Stroke* **16**, 321–341 (2021).
124. Tsivgoulis, G. et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. *Ann. Neurol.* **84**, 694–704 (2018).
125. Goeldlin, M. B. et al. Intracerebral haemorrhage volume, haematoma expansion and 3-month outcomes in patients on antiplatelets. A systematic review and meta-analysis. *Eur. Stroke J.* **6**, 333–342 (2021).
126. Christensen, H. et al. European stroke organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. *Eur. Stroke J.* **4**, 294–306 (2019).
127. Baharoglu, M. I. et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet* **387**, 2605–2613 (2016).
128. Sondag, L. et al. Variation in medical management and neurosurgical treatment of patients with supratentorial spontaneous intracerebral haemorrhage. *Eur. Stroke J.* **6**, 134–142 (2021).
129. Desborough, M. J. R. et al. Desmopressin for patients with spontaneous intracerebral haemorrhage taking antiplatelet drugs (DASH): a UK-based, phase 2, randomised, placebo-controlled, multicentre feasibility trial. *Lancet Neurol.* **22**, 557–567 (2023).
130. Siepen, B. M. et al. Intracerebral haemorrhage in patients taking different types of oral anticoagulants: a pooled individual patient data analysis from two national stroke registries. *Stroke Vasc. Neurol.* https://doi.org/10.1136/svn-2023-002813 (2024).
131. Steiner, T. et al. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *Lancet Neurol.* **15**, 566–573 (2016).
132. Kuramatsu, J. B. et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA.* **313**, 824–836 (2015).
133. Sheth, K. N. et al. Time to anticoagulation reversal and outcomes after intracerebral hemorrhage. *JAMA Neurol.* **81**, 363–372 (2024).
134. Demchuk, A. M. et al. Hemostatic efficacy and anti-FXa (factor Xa) reversal with andexanet alfa in intracranial hemorrhage: ANNEXA-4 substudy. *Stroke* **52**, 2096–2105 (2021).
135. Pollack, C. V. Jr., Reilly, P. A. & Weitz, J. I. Dabigatran reversal with idarucizumab. *N. Engl. J. Med.* **377**, 1691–1692 (2017).
136. Huttner, H. B. et al. Hematoma expansion and clinical outcomes in patients with factor-Xa inhibitor-related atraumatic intracerebral hemorrhage treated within the ANNEXA-4 trial versus real-world usual care. *Stroke* **53**, 532–543 (2022).
137. Connolly, S. J. et al. Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage. *N. Engl. J. Med.* **390**, 1745–1755 (2024).
138. Polymeris, A. A. et al. Tranexamic acid for intracerebral hemorrhage in patients on non-vitamin K antagonist oral anticoagulants (TICH-NOAC): a multicenter, randomized, placebo-controlled, phase 2 trial. *Stroke* **54**, 2223–2234 (2023).
139. Connolly, S. J. et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N. Engl. J. Med.* **380**, 1326–1335 (2019).
140. Siepen, B. M. et al. Andexanet alfa vs non-specific treatments for intracerebral hemorrhage in patients taking factor Xa inhibitors — individual patient data analysis of ANNEXA-4 and TICH-NOAC. *Int. J. Stroke* https://doi.org/10.1177/17474930241230209 (2024).
141. Demchuk, A. M. et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study. *Lancet Neurol.* **11**, 307–314 (2012).
142. Sprigg, N. et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet* **391**, 2107–2115 (2018).
143. Meretoja, A. et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol.* **19**, 980–987 (2020).
144. Liu, J. et al. Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE): a multicentre, randomised, placebo-controlled trial. *Stroke Vasc. Neurol.* **6**, 160–169 (2021).
145. Yassi, N. et al. Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2h of symptom onset (STOP-MSU): an international, double-blind, randomised, phase 2 trial. *Lancet Neurol.* **23**, 577–587 (2024).
146. Mayer, S. A. et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N. Engl. J. Med.* **358**, 2127–2137 (2008).
147. Gladstone, D. J. et al. Effect of recombinant activated coagulation factor vii on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: the SPOTLIGHT and STOP-IT randomized clinical trials. *JAMA Neurol.* **76**, 1493–1501 (2019).
148. Yogendrakumar, V., Mayer, S. A., Steiner, T., Broderick, J. P. & Dowlatshahi, D. Exploring hematoma expansion shift with recombinant factor VIIa: a pooled analysis of 4 randomized controlled trials. *Stroke* **54**, 2990–2998 (2023).
149. ISRCTN Registry. Tranexamic acid for very early bleeds in the brain. https://doi.org/10.1186/ISRCTN97695350 (2024).
150. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT05836831 (2024).
151. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03044184 (2019).
152. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT04742205 (2024).
153. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03496883 (2024).
154. Eilertsen, H. et al. Haemostatic therapies for stroke due to acute, spontaneous intracerebral haemorrhage. *Cochrane Database Syst. Rev.* **10**, Cd005951 (2023).
155. Sun, S. et al. The effect of mannitol in the early stage of supratentorial hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. *World Neurosurg.* https://doi.org/10.1016/j.wneu.2018.11.249 (2018).
156. Shah, M. et al. Effect of hyperosmolar therapy on outcome following spontaneous intracerebral hemorrhage: Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study. *J. Stroke Cerebrovasc. Dis.* **27**, 1061–1067 (2018).
157. Wintzer, S., Heckmann, J. G., Huttner, H. B. & Schwab, S. Dexamethasone in patients with spontaneous intracerebral hemorrhage: an updated meta-analysis. *Cerebrovasc. Dis.* **49**, 495–502 (2020).
158. Chang, J. J. et al. Minocycline and matrix metalloproteinase inhibition in acute intracerebral hemorrhage: a pilot study. *Eur. J. Neurol.* **24**, 1384–1391 (2017).
159. Fouda, A. Y. et al. Minocycline in acute cerebral hemorrhage: an early phase randomized trial. *Stroke* **48**, 2885–2887 (2017).
160. Fu, Y. et al. Fingolimod for the treatment of intracerebral hemorrhage: a 2-arm proof-of-concept study. *JAMA Neurol.* **71**, 1092–1101 (2014).
161. Selim, M. et al. Deferoxamine mesylate in patients with intracerebral haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial. *Lancet Neurol.* **18**, 428–438 (2019).
162. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT04088630 (2024).
163. Gao, D. et al. Statins for neuroprotection in spontaneous intracerebral haemorrhage (STATIC): protocol for a multicentre, prospective and randomised controlled trial. *BMJ open.* **14**, e079879 (2024).
164. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT04890379 (2023).
165. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03463317 (2021).
166. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT05263167 (2022).
167. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT05066620 (2021).
168. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT05369351 (2024).
169. US National Library of Medicine.*ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT05434065 (2024).

170. De Herdt, V. et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. *Neurology* **77**, 1794–1800 (2011).
171. Peter-Derex, L. et al. Safety and efficacy of prophylactic levetiracetam for prevention of epileptic seizures in the acute phase of intracerebral haemorrhage (PEACH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* **21**, 781–791 (2022).
172. Tran, Q. K. et al. Preventing seizure occurrence following spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of seizure prophylaxis. *Seizure* **87**, 46–55 (2021).
173. Sondag, L. et al. Neurosurgical intervention for supratentorial intracerebral hemorrhage. *Ann. Neurol.* **88**, 239–250 (2020).
174. Gregson, B. A. et al. Volume reduction with surgery for ICH: when is it effective? Analysis of the CT scans from the STICH II trial. *Br. J. Neurosurg.* 1–8 https://doi.org/10.1080/02688697.2023.2207643 (2023).
175. Polster, S. P. et al. Intracerebral hemorrhage volume reduction and timing of intervention versus functional benefit and survival in the MISTIE III and STICH trials. *Neurosurgery* **88**, 961–970 (2021).
176. Morgenstern, L. B., Demchuk, A. M., Kim, D. H., Frankowski, R. F. & Grotta, J. C. Rebleeding leads to poor outcome in ultra-early craniotomy for intracerebral hemorrhage. *Neurology* **56**, 1294–1299 (2001).
177. Sondag, L. et al. Safety and technical efficacy of early minimally invasive endoscopy-guided surgery for intracerebral haemorrhage: the Dutch Intracerebral haemorrhage Surgery Trial pilot study. *Acta Neurochir.* **165**, 1585–1596 (2023).
178. Kuo, L. T. et al. Early endoscope-assisted hematoma evacuation in patients with supratentorial intracerebral hemorrhage: case selection, surgical technique, and long-term results. *Neurosurg. Focus.* **30**, E9 (2011).
179. Kellner, C. P. et al. Time to evacuation and functional outcome after minimally invasive endoscopic intracerebral hemorrhage evacuation. *Stroke* **52**, e536–e539 (2021).
180. Dammers, R., Beck, J., Volovici, V., Anderson, C. S. & Klijn, C. J. M. Advancing the surgical treatment of intracerebral hemorrhage: study design and research directions. *World Neurosurg.* **161**, 367–375 (2022).
181. Pradilla, G. et al. Trial of early minimally invasive removal of intracerebral hemorrhage. *N. Engl. J. Med.* **390**, 1277–1289 (2024).
182. Beck, J. et al. Decompressive craniectomy plus best medical treatment versus best medical treatment alone for spontaneous severe deep supratentorial intracerebral haemorrhage: a randomised controlled clinical trial. *Lancet* **403**, 2395–2404 (2024).
183. Klijn, C. J., Dammers, R. & Sprigg, N. Decompressive craniectomy for deep intracerebral haemorrhage: a SWITCH towards better outcomes? *Lancet* **403**, 2351–2353 (2024).
184. Lin, J. & Frontera, J. A. Decompressive hemicraniectomy for large hemispheric strokes. *Stroke* **52**, 1500–1510 (2021).
185. Kuramatsu, J. B. et al. Association of surgical hematoma evacuation vs conservative treatment with functional outcome in patients with cerebellar intracerebral hemorrhage. *JAMA* **322**, 1392–1403 (2019).
186. Banerjee, G. et al. Longer term stroke risk in intracerebral haemorrhage survivors. *J. Neurol. Neurosurg. Psychiatry* **91**, 840–845 (2020).
187. Li, L. et al. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *Lancet Neurol.* **20**, 437–447 (2021).
188. Boe, N. J. et al. Major cardiovascular events after spontaneous intracerebral hemorrhage by hematoma location. *JAMA Netw. open.* **6**, e235882 (2023).
189. Fandler-Höfler, S., Gattringer, T., Enzinger, C. & Werring, D. J. Comparison of Boston criteria v2.0/v1.5 for cerebral amyloid angiopathy to predict recurrent intracerebral hemorrhage. *Stroke* **54**, 1901–1905 (2023).
190. Duering, M. et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol.* **22**, 602–618 (2023).
191. Wiegertjes, K. et al. Diffusion-weighted imaging lesions and risk of recurrent stroke after intracerebral haemorrhage. *J. Neurol. Neurosurg. Psychiatry* **92**, 950–955 (2021).
192. Murthy, S. B. et al. Diffusion-weighted imaging lesions after intracerebral hemorrhage and risk of stroke: a MISTIE III and ATACH-2 analysis. *Stroke* **52**, 595–602 (2021).
193. Murthy, S. B. et al. Association between intracerebral hemorrhage and subsequent arterial ischemic events in participants from 4 population-based cohort studies. *JAMA Neurol.* **78**, 809–816 (2021).
194. Fischer, U. et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. *Lancet Neurol.* **13**, 374–384 (2014).
195. Biffi, A. et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA* **314**, 904–912 (2015).
196. Biffi, A. et al. Impact of uncontrolled hypertension at 3 months after intracerebral hemorrhage. *J. Am. Heart Assoc.* **10**, e020392 (2021).
197. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* **358**, 1033–1041 (2001).
198. Benavente, O. R. et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* **382**, 507–515 (2013).
199. Kitagawa, K. et al. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: a randomized clinical trial and meta-analysis. *JAMA Neurol.* **76**, 1309–1318 (2019).
200. Teo, K. C. et al. Blood pressure control targets and risk of cardiovascular and cerebrovascular events after intracerebral hemorrhage. *Stroke* **54**, 78–86 (2023).
201. Anderson, C. S. et al. Triple therapy prevention of recurrent intracerebral disease events trial: rationale, design and progress. *Int. J. Stroke* **17**, 1156–1162 (2022).
202. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03863665 (2021).
203. RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet* https://doi.org/10.1016/s0140-6736(19)30840-2 (2019).
204. Al-Shahi Salman, R. et al. Effects of antiplatelet therapy after stroke caused by intracerebral hemorrhage: extended follow-up of the RESTART randomized clinical trial. *JAMA Neurol.* **78**, 1179–1186 (2021).
205. Al-Shahi Salman, R. et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *Lancet Neurol.* **18**, 643–652 (2019).
206. ISRCTN Registry. The use of aspirin or clopidogrel for people who survive stroke due to bleeding in the brain. https://doi.org/10.1186/ISRCTN16705062 (2024).
207. Biffi, A. et al. Oral anticoagulation and functional outcome after intracerebral hemorrhage. *Ann. Neurol.* **82**, 755–765 (2017).
208. Schreuder, F. et al. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): a randomised, open-label, phase 2 trial. *Lancet Neurol.* **20**, 907–916 (2021).
209. Effects of oral anticoagulation for atrial fibrillation after spontaneous intracranial haemorrhage in the UK: a randomised, open-label, assessor-masked, pilot-phase, non-inferiority trial. *Lancet Neurol.* **20**, 842–853 (2021).
210. Al-Shahi Salman, R. et al. Effects of oral anticoagulation in people with atrial fibrillation after spontaneous intracranial haemorrhage (COCROACH): prospective, individual participant data meta-analysis of randomised trials. *Lancet Neurol.* **22**, 1140–1149 (2023).
211. Shoamanesh, A. Anticoagulation in patients with cerebral amyloid angiopathy. *Lancet* **402**, 1418–1419 (2023).
212. Cresti, A. et al. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroInterventi* **15**, e225–e230 (2019).
213. Osmancik, P. et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J. Am. Coll. Cardiol.* **75**, 3122–3135 (2020).
214. Reddy, V. Y. et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* **312**, 1988–1998 (2014).
215. Holmes, D. R. et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* **374**, 534–542 (2009).
216. Horstmann, S. et al. Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. *Neurology* **82**, 135–138 (2014).
217. Schrag, M. et al. Left atrial appendage closure for patients with cerebral amyloid angiopathy and atrial fibrillation: the LAA-CAA cohort. *Transl. Stroke Res.* https://doi.org/10.1007/s12975-020-00838-5 (2020).
218. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03243175 (2023).
219. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT02830152 (2024).
220. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT02928497 (2024).
221. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT04676880 (2024).
222. Kittner, S. J. et al. Ethnic and racial variation in intracerebral hemorrhage risk factors and risk factor burden. *JAMA Netw. Open.* **4**, e2121921 (2021).
223. Lioutas, V. A. et al. Assessment of incidence and risk factors of intracerebral hemorrhage among participants in the Framingham Heart Study between 1948 and 2016. *JAMA Neurol.* **77**, 1252–1260 (2020).
224. Amarenco, P. et al. High-dose atorvastatin after stroke or transient ischemic attack. *N. Engl. J. Med.* **355**, 549–559 (2006).
225. Chaturvedi, S. et al. Effect of atorvastatin in elderly patients with a recent stroke or transient ischemic attack. *Neurology* **72**, 688–694 (2009).
226. Rosenson, R. S. & Tangney, C. C. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. *JAMA* **279**, 1643–1650 (1998).
227. Takemoto, M. & Liao, J. K. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. *Arterioscler. Thromb. Vasc. Biol.* **21**, 1712–1719 (2001).
228. Undas, A., Celińska-Löwenhoff, M., Kaczor, M. & Musial, J. New nonlipid effects of statins and their clinical relevance in cardiovascular disease. *Thromb. Haemost.* **91**, 1065–1077 (2004).
229. Falcone, G. J. et al. Genetically elevated LDL associates with lower risk of intracerebral hemorrhage. *Ann. Neurol.* **88**, 56–66 (2020).
230. Georgakis, M. K. et al. Genetic determinants of blood lipids and cerebral small vessel disease: role of high-density lipoprotein cholesterol. *Brain* **143**, 597–610 (2020).
231. Ma, C. et al. Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage: a prospective study. *Neurology* **93**, e445–e457 (2019).
232. Mayerhofer, E. et al. Genetically predicted on-statin LDL response is associated with higher intracerebral haemorrhage risk. *Brain* **145**, 2677–2686 (2022).
233. Yu, Z. et al. Lipids, apolipoproteins, statins, and intracerebral hemorrhage: a Mendelian randomization study. *Ann. Neurol.* **92**, 390–399 (2022).

234. Ziff, O. J., Banerjee, G., Ambler, G. & Werring, D. J. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* **90**, 75–83 (2019).
235. Boe, N. J. et al. Association between statin use and intracerebral hemorrhage location: a nested case–control registry study. *Neurology* **100**, e1048–e1061 (2023).
236. Amarenco, P. et al. A comparison of two LDL cholesterol targets after ischemic stroke. *N. Engl. J. Med.* **382**, 9 (2020).
237. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT03936361 (2024).
238. Sanz-Cuesta, B. E. & Saver, J. L. Lipid-lowering therapy and hemorrhagic stroke risk: comparative meta-analysis of statins and PCSK9 inhibitors. *Stroke* **52**, 3142–3150 (2021).
239. van Middelaar, T. et al. Effect of antihypertensive medication on cerebral small vessel disease: a systematic review and meta-analysis. *Stroke* **49**, 1531–1533 (2018).
240. Lai, Y. et al. Effect of intensive blood pressure control on the prevention of white matter hyperintensity: systematic review and meta-analysis of randomized trials. *J. Clin. Hypertens.* **22**, 1968–1973 (2020).
241. Wardlaw, J. M. et al. Isosorbide mononitrate and cilostazol treatment in patients with symptomatic cerebral small vessel disease: the Lacunar Intervention Trial-2 (LACI-2) randomized clinical trial. *JAMA Neurol.* **80**, 682–692 (2023).
242. Markus, H. S. et al. Framework for clinical trials in cerebral small vessel disease (FINESSE): a review. *JAMA Neurol.* **79**, 1187–1198 (2022).
243. Leurent, C. et al. Immunotherapy with ponezumab for probable cerebral amyloid angiopathy. *Ann. Clin. Transl. Neurol.* **6**, 795–806 (2019).
244. Greenberg, S. M. et al. A phase 2 study of tramiprosate for cerebral amyloid angiopathy. *Alzheimer Dis. Assoc. Disord.* **20**, 269–274 (2006).
245. Chauhan, N. B. & Siegel, G. J. Antisense inhibition at the β-secretase-site of β-amyloid precursor protein reduces cerebral amyloid and acetyl cholinesterase activity in Tg2576. *Neuroscience* **146**, 143–151 (2007).
246. van Veluw, S. J. et al. Vasomotion as a driving force for paravascular clearance in the awake mouse brain. *Neuron* **105**, 549–561.e5 (2020).
247. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/study/NCT06393712 (2024).
248. Mutimer, C. A. et al. Cerebral amyloid angiopathy and the fibrinolytic system: is plasmin a therapeutic target? *Stroke* **52**, 2707–2714 (2021).
249. Voigt, S. et al. Minocycline for sporadic and hereditary cerebral amyloid angiopathy (BATMAN): study protocol for a placebo-controlled randomized double-blind trial. *Trials* **24**, 378 (2023).
250. Bax, F. et al. Minocycline in severe cerebral amyloid angiopathy: a single-center cohort study. *J. Am. Heart Assoc.* **13**, e033464 (2024).

Author contributions

S.F.-H., M.B.G., W.M.T.J. and D.J.W. researched data for the article and contributed substantially to discussion of the content. D.J.S., S.F.-H., M.B.G., W.M.T.J., C.J.M.K. and D.J.W. wrote the article. S.F.-H., Y.D., M.B.G., W.M.T.J. and D.J.W. reviewed and/or edited the manuscript before submission. D.J.S., S.F-H., C.J.M.K. and D.J.W. contributed equally.

Competing interests

DJW reports speaking honoraria from Bayer; speaking and chairing honoraria from Alexion and NovoNordisk; and consultancy fees from Alnylam, Bayer and NovoNordisk. He is Co-Chief Investigator for the PROHIBIT-ICH trial. He has participated as a member of the LACI-2, TICH-2, TICH-3, RESTART, MACE-ICH and PLINTH Trial Steering Committees. The other authors declare no competing interests.

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[1]Department of Neurology, Inselspital University Hospital Bern and University of Bern, Bern, Switzerland. [2]Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK. [3]Department of Neurology, Medical University of Graz, Graz, Austria. [4]Department of Neurology, Xiangya Hospital of Central South University, Changsha, Hunan, China. [5]Department of Neurology, Isala Hospital, Zwolle, Netherlands. [6]Department of Neurology, Donders Institute of Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, Netherlands. [7]These authors contributed equally: David J. Seiffge, Simon Fandler-Höfler, Catharina J. M. Klijn, David J. Werring.